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 #:	21-883
Drug Name:	Dalvance™ (Dalbavancin hydrochloride) for Injection
Indication:	Acute bacterial skin and skin structure infections (ABSSSI)
Applicant:	Durata Therapeutics, Inc.
Stamp Date:	September 26, 2013
PDUFA Goal Date:	May 26, 2014
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1. EXECUTIVE SUMMARY

Trials 301 and 302 both met their primary objectives of demonstrating non-inferiority of dalbavancin (Dalvance™) to comparator therapy (vancomycin/linezolid) based on early clinical response at 48-72 hours using a 10% margin. Therefore, overall evidence of efficacy was considered to be adequate. However, there is still some uncertainty regarding the efficacy at later endpoints, such as clinical status at end of treatment (EOT) evaluated on Day 14-15 and clinical status at short term follow-up (SFU) evaluated on Day 26-30, which were highly variable across the two trials, favoring the comparator in Trial 301 and dalbavancin in Trial 302, **Table 12**. In order to be more consistent with the expected disease progression of ABSSSIs at later time points, the Reviewer conducted sensitivity analyses which included additional success criteria considered to be clinically more relevant. The Reviewer also conducted concordance analyses which considered findings at later assessments among patients who were responders at 48-72 hours. Key efficacy findings for Trials 301 & 302 are summarized below.

Primary analyses of patients achieving cessation of spread of lesion and absence of fever at 48-72 hours (responders) showed treatments to be similar in both trials based on a non-inferiority (NI) design using a margin of 10%. The responder rate was 83.3% in the dalbavancin arm compared to 81.8% in the comparator arm resulting in a treatment difference of 1.5% (95% confidence interval (CI): (-4.6%, 7.9%) in Trial 301. In Trial 302, the responder rate was 76.8% in the dalbavancin arm compared to 78.3% in the comparator arm resulting in a difference of -1.5% (95% CI: -7.4%, 4.6%), **Table 11**. When defining responders based on a 20% reduction in lesion area without the fever component (based on current ABSSSI guidance) treatments were also similar at 89.9% vs. 90.9%, a difference of -1.0% (95% CI: -5.7%, 4.0%) in Trial 301 and 87.6% vs. 85.9%, 1.7% (-3.2%, 6.7%) in Trial 302. Overall, early efficacy findings supported the non-inferiority of dalbavancin to the comparator at 48-72 hours since the lower 95% confidence limit was above -10% for the primary and key secondary endpoints of both trials. Comparisons of the distributions of patients in each treatment arm meeting various percentage reductions in lesion area at 48-72 hours were also found to be supportive of non-inferiority, **Figure 3**.

For success rates in clinical status at EOT and SFU, Trial 301 comparisons were 81.3% vs. 86.7%, -5.4% (-11.5%, 0.6%) and 83.7% vs. 88.1%, -4.4% (-10.2%, 1.3%), respectively, while Trial 302 comparisons were 88.7% vs. 85.3%, 3.4% (-1.5, 8.3) and 88.1% vs. 84.5%, 3.6% (-1.3, 8.7), **Table 12**. However, interpretability of these findings may be limited by the success criteria used in the clinical status endpoints since these criteria may fail to address the appropriate degree of improvement in local signs that would be expected at later assessments. For example, the success criteria used for lesion area/erythema at EOT and SFU only required a decrease (i.e. any magnitude of decrease) in lesion size which is inconsistent with the requirement of at least a 20% reduction in lesion area at an earlier time point (i.e. at 48-72 hours) under the current ABSSSI guidance[1]. In order to be more consistent with the expected disease progression of ABSSSIs at later time points, the Reviewer conducted sensitivity analyses which included additional success criteria thought to be clinically more relevant. When considering these success criteria in the clinical status endpoint, treatment differences became even larger (less favorable for dalbavancin) in Trial 301 and smaller (more similar to comparator) in Trial 302, as shown in **Table 13.**

Comparisons of the distributions of patients in each treatment arm meeting various percentage reductions in lesion area at EOT and SFU showed similar trends, **Figure 4**. Other sensitivity analyses in Trial 301 also showed substantial treatment differences at later endpoints, including concordance analyses of responders at 48-72 hours with clinical success at EOT (**Table 23**) and responders at 48-72 hours with complete resolution of local signs at SFU (**Table 25**), and analyses of success rates in patients with *Staphylococcus aureus* at baseline, **Table 21**. However, these sensitivity analyses in Trial 302 did not show similar differences.

2. INTRODUCTION

2.1 Overview

Background

In this 505(b)(1) NDA submission, Durata Therapeutics, Inc. is seeking approval of dalbavancin (Dalvance™), a new molecular entity for the treatment of acute bacterial skin and skin structure infections (ABSSSI) known or suspected to be caused by gram-positive organisms. To support the efficacy and safety of Dalvance™, Durata has submitted results from two pivotal Phase 3 randomized, double-blind, double-dummy, multi-center trials (Trials DUR001-301 & DUR001-302, hereafter referred to as Trials 301 & 302), as well as a randomized double-blind Phase 3 legacy study in complicated skin and skin structure infections (Study VER001-9). Due to the limitations in the design and endpoints of Study VER001-9, this statistical review focuses on evidence obtained from the two pivotal trials for ABSSSI, Trials 301 & 302.

Similar in design, Trials 301 & 302 both closely followed the 2010 FDA ABSSSI guidance[2] and were reviewed under a special protocol assessment (SPA). Both trials compared dalbavancin (1000mg IV infusion on Day 1 and a second 500mg IV infusion on Day 8) to a 10-14 day regimen of vancomycin (1000mg or 15mg/kg IV infusion q12h for at least 3 days followed by a possible switch to oral linezolid, 600 mg q12h). Both trials also evaluated the primary endpoint of early clinical response (i.e. responder rates) in the intent-to-treat (ITT) population where responders had to achieve cessation of spread of erythema at the lesion site along with absence of fever at 48-72 hours from baseline. This endpoint was evaluated under a non-inferiority (NI) design with a pre-specified margin of 10%. A 10% NI margin is supported by findings from two historical studies (Snodgrass et. al, 1937)[3,4] comparing sulfonamides to UV light in patients diagnosed with erysipelas at the 48-72 hour time points.

Although the Agency agreed to the design and endpoints of Trials 301 & 302 under an SPA, the Agency is currently recommending a different primary endpoint for future ABSSSI trials. As outlined in the recent ABSSSI guidance[1], this primary endpoint requires responders to have at least a 20% reduction in lesion area at 48-72 hours with no fever component. This endpoint can also be tested for non-inferiority using a 10% margin.

History of Product Development

The following is a timeline of some of the notable events in the history of product development for Dalbavancin.

- The dalbavancin NDA 21-883 was previously submitted on December 21, 2004 by Vicuron, a subsidiary of Pfizer.
- The Agency issued approvable letters on September 21, 2005, June 21, 2006, and December 20, 2007
- The NDA was previously withdrawn by Pfizer on September 15, 2008
- The Division was notified that Durata assumed responsibility for management of IND 60,613 and the future development of dalbavancin on January 25, 2010
- An End of Phase 2 meeting was held with Durata on June 3, 2010
- A SPA resubmission letter was issued on June 22, 2011
- Dalbavancin was given Qualified Infectious Disease Product (QIDP) designation for the treatment of ABSSSI on October 25, 2012.
- A pre-NDA meeting was held on June 26, 2013.
- NDA 21883 was re-submitted on September 26, 2013
- An SPA Agreement letter was issued on March 21, 2013 for a clinical trial protocol, "A phase 3b, double-blind, multicenter, randomized, NI trial to compare the efficacy and safety of single dose dalbavancin to a two dose regimen of dalbavancin for the treatment of ABSSSI."
- An Anti-infective Drugs Advisory Committee *(*AIDAC) meeting was held to discuss NDA 21883 on March 31, 2014.

Reviewer Comments: *As Dalvance™ is a new molecular entity, this NDA submission was discussed at an Anti-Infective Drugs Advisory Committee (AIDAC) meeting on March 31, 2014. The committee voted unanimously (12 votes to 0) that Dalvance™ was safe and effective in treating patients with ABSSSI. In stating their reasons for voting in favor of the efficacy of Dalvance™, several committee members pointed to the fact that both trials (i.e. Trials 301 and 302) met their respective primary endpoints.*

Overview of Trials 301 & 302

A brief overview of the two identical pivotal Phase 3 clinical trials for ABSSSI, Trials 301 & 302, is provided in **Table 1**. The two trials share many of the same design characteristics; however, Trial 302 was substantially larger. Both trials had pre-specified interim analyses with the potential for sample size re-estimation (SSR) with SSR only being performed in Trial 302. These interim analyses are discussed further in Section 3.2.3 of this review.

Table 1: Comparison of Trials 301 & 302

	Trial 301	Trial 302
Type of Trial:	Phase 3 multicenter, randomized, double-blind comparative trial to evaluate the safety and efficacy of dalbavancin vs. vancomycin + linezolid in adults with ABSSSI	
Objective:	Demonstrate noninferiority (NI) in early clinical response of dalbavancin treatment vs. vancomycin plus linezolid in adults with ABSSSI. The NI margin was pre-specified at 10%.	
Treatment Arms:	Two arms: IV dalbavancin (1000mg on Day 1 & 500mg on Day 8)[1] and IV vancomycin plus oral linezolid (1000mg or 15mg/kg vancomycin for 3 to 14 days plus linezolid 600mg q12h)	
Sample Size:	573 ITT patients[2]	739 ITT patients[2]
Primary Endpoint:	Early clinical response at 48-72 hours in ITT subjects	
Study Design:	Baseline: within 24 hours of first dose of study drug, randomization Study drug administration: Day 1 to EOT (for 10 to 14 days) EOT: Day 14-15 SFU: Day 28 Long term follow-up (LFU): Day 70	
Statistical Methods:	The observed treatment difference in response with 95% confidence interval (CI) computed stratifying for the presence or absence of fever at Baseline. If the lower limit of the 95% CI for the difference in response rates was greater than -10%, the non-inferiority of dalbavancin to vancomycin/linezolid was concluded.	

[1] Patients with creatinine clearance values < 30 mL/min not receiving hemodialysis or peritoneal dialysis received reduced dalbavancin doses of 750 mg on Day 1 and 375 mg on Day 8.
[2] A blinded SSR was performed when 60% of patients had early clinical response data available.
Source: Reviewer Table

2.2 Data Sources

The reviewer primarily considered the clinical summary of efficacy, clinical study reports and selected datasets which are described below for Trial 301 along with their links. Datasets in Trials 301 and 302 were structured similarly and following the same naming conventions. The data formats used in this submission were SDTM and ADAM. (Note: Replacing '301' with '302' in the links below will provide the correct link for Trial 302).

- Clinical Summary of Efficacy : \\cdsesub1\evsprod\NDA021883\0000\m2\27-clin-summary
- Clinical Study Reports: \\cdsesub1\evsprod\NDA021883\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\absssi\5351-stud-rep-contr\dur001-301
- Datasets: \\cdsesub1\evsprod\NDA021883\0000\m5\datasets\dur001-301\analysis\adam\datasets

- ADSL- Demographic and Baseline Characteristics
- ADCM- Concomitant Medications
- ADCMAB- Antibiotics/Antipyretics/NSAIDs/Pain
- ADABS- Description and Measurements of ABSSSI
- ADISA- Local signs and symptoms
- ADEFF- Efficacy Outcome - Clinical Response

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the data quality was acceptable. No errors were noted in any of the submitted datasets. Datasets and variables were clearly described and well-documented. The Reviewer could reproduce all major analyses.

However, there were some weaknesses with respect to the usability of the data at a few sites, as described below:

- **Data from Six patients in Trial 301:** The Office of Scientific Investigations (OSI) found that 6 patients from Site 118 in Trial 301 lacked drug administration records and stated that these patients may be excluded at the Division's discretion, although no data integrity issues were reported (Clinical Inspection Summary (Addendum) by Dr. Iacono-Connors, OSI on May 6, 2014). Therefore, sensitivity analyses excluding these 6 patients were conducted. These analyses showed similar results at 48-72 hours at 83.0% vs. 82.0%, 1.0% (-5.1%, 7.4%) for the primary endpoint and 89.8% vs. 90.8%, -1.1% (-5.9%, 4.0%) when defining responders based on a 20% reduction in lesion area, **Table 34**. However, Trial 301 comparisons at later endpoints became slightly less favorable at 80.9% (dalbavancin) vs. 87.0% (comparator), a difference of -6.1% (95% CI: -12.2, -0.0) at EOT and 83.4% vs. 88.4%, -5.0% (-10.8, 0.8) at SFU, **Table 35**. Prior to these exclusions, treatment differences were -5.4% (-11.5, 0.6) at EOT and -4.4% (-10.2%, 1.3%), **Table 12**.

  Reviewer Comments: *OSI had previously considered all data from sites 112, 118 and 122 (23 patients) of Study 301 to be unreliable based on the Clinical Inspection Summary by Dr. Iacono-Connors, OSI on April 11, 2014. However, OSI had upgraded the status of these sites from OAI (Official Action Indicated) to VAI (Voluntary Action Indicated) and considered their data reliable except for the 6 patients from Site 118 with missing drug administration records (noted above).*

The Reviewer also noted the following inconsistencies with data obtained from a few other sites:

- **Investigator errors measuring lesion size resulting in study biases:** Lesion measurements observed in Trial 302 suggested potential errors. For example, comparing proportions of patients with reductions in lesion area of exactly 0% at 48-72 hours, Trial 302 showed 15 patients with exactly a 0% reduction vs. no patients in Trial 301. In addition, Trial 302 Site 903 (Estonia) showed 10 of 15 patients with a 0% reduction from baseline at 48-72 hours.

Measurement error can make treatments appear to be more similar when in fact they are not and this can result in study biases under a non-inferiority design.

- **Unusually High Responder Rates at Study Sites:** In Trial 301, Site 607 (Ukraine) showed responder rates at 48-72 hours of 36/36 (100%) for dalbavancin vs. 47/48 (97.9%) for the comparator. Comparisons of overall response rates for Site 607 vs. All Other Sites were 98.8% vs. 79.8%, 19.1% (13.3, 23.2), p-value= $1.2x10^{-6}$ using Fisher's exact test.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

Treatment Arms: Patients were randomly assigned to receive in a 1:1 ratio either two IV doses of dalbavancin or 10 to 14 days of IV vancomycin/oral linezolid. Following at least 72 hours of study drug treatment, patients could have been switched from q12h IV study drug (either dalbavancin and placebo or vancomycin and placebo) to oral therapy for patients in the vancomycin/linezolid treatment group or matching placebo for patients in the dalbavancin treatment group, if the criteria for IV to oral switch had been met. The planned dosing schedule is summarized in **Table 2.**

Table 2: Study Dosing Schedule

	Dalbavancin Arm	**Vancomycin/Linezolid Arm**
Day 1	IV dalbavancin, 1000mg[1] AND Matching IV placebo, q12h	IV placebo to match dalbavancin AND IV vancomycin 1000mg or 15mg/kg q12h[2]
Day 2-3	IV placebo q12h to match vancomycin	IV vancomycin 1000mg or 15mg/kg q12h[2]
Day 8	IV dalbavancin, 500mg[1]	IV placebo to match dalbavancin
Days 4-14[3]	IV placebo q12h to match vancomycin OR oral placebo q12h to match linezolid	IV vancomycin 1000mg or 15mg/kg q12h[2] OR Oral linezolid 600mg q12h

[1] If CrCl < 30mL/min, doses were 750mg on Day 1 and 375 mg on Day 8
[2] Dependent on study site standard of care, dose was adjusted as appropriate for CrCl values, renal function and vancomycin level
[3] After at least 72 hours of treatment, patients randomly assigned to vancomycin could have been switched to oral linezolid
Source: Partially Adapted from Table 9.1 in CSR for Trial 301 & 302

Design: Trials 301 & 302 are both Phase 3, multisite, double-blind, double-dummy, randomized, controlled trials comparing dalbavancin with a regimen of vancomycin followed by a possible switch to oral linezolid for patients with ABSSSI known or suspected to be caused by gram-positive bacteria. The initial sample size for Trial 301 & Trial 302 was planned to be 556 randomly assigned patients in the ITT population. In both trials, an interim analysis for sample size re-estimation was performed when early clinical response data at 48 to 72 hours were available for approximately 60% of the patients (334 patients). However, the sample size

increase was only recommended in Trial 302 which enrolled 739 patients in order to maintain 90% study power.

Baseline assessments were performed within 24 hours before the first dose. Patients were randomly assigned to one of two treatment groups on Day 1, within 4 hours before their first dose of Study drug. On Day 1, patient IV treatment was initiated and temperature was recorded. Efficacy assessments were made on Days 2, 3, 4, 8, and 14 or 15 of the treatment period. Safety assessments were made at every visit. An EOT visit took place on Days 14 or 15, or within 3 days following premature discontinuation of treatment. An SFU visit was planned for Day 28 and a final long-term follow-up visit (LFU) at Day 70. **Table 3** shows the efficacy and safety assessments made in these visits.

Table 3: Overall Study Design (Trials 301 & 302)

Study Days	**Dosing Administration/Study Visit**
Days -1 to 1	• Baseline Assessments • Randomization (4 hours before first dose)
Days 1 to 3	• IV dalbavancin or placebo (Day 1) • IV vancomycin or placebo (Days 1-3) • Efficacy assessments (Day 2 and 3)
Days 4 to 14	• Efficacy assessments (Day 4, 8 and 14) • IV vancomycin or placebo OR Oral linezolid or placebo (Day 4 to Day 10-14)
Days 14 to 15	• End of treatment Visit (EOT)[1]
Day 28[3]	• Short-term follow up Visit (SFU)
Day 70[4]	• Long-term follow up Visit (LFU)

[1] If treatment was prematurely discontinued, the EOT was scheduled within 3 days of discontinuation
[2] Safety assessments were made at all visits.
[3] The SFU visit was targeted for Day 28, but may have occurred from Day 26 through Day 30.
[4] The LFU visit was targeted for Day 70, but may have occurred from Day 60 through Day 88.
Source: Partially Adapted from Figure 9.1 in CSR for Trial 301 & 302

Inclusion Criteria:
The Reviewer's description of the Applicant's inclusion criteria is shown below:
1. Male or female patients 18 to 85 years of age.
2. Patient must give informed consent.
3. Patients having an ABSSSI defined as an infection either involving deeper soft tissue or requiring significant surgical intervention:
   a. Major cutaneous abscess characterized as a collection of pus within the dermis or deeper that was accompanied by erythema, edema and/or induration which:
      - required surgical incision and drainage, and
      - was associated with cellulitis such that the total affected area involved at least

75 cm^2 of erythema, and was defined by a margin of erythema that was ≥5 cm from the rim of induration or edema that defined the border of the abscess in all directions, or,
- alternatively, involved the central face and was associated with an area of erythema of at least 50 cm^2 and a margin ≥3 cm in all directions from the abscess rim.

b. Surgical site or traumatic wound infection characterized by purulent drainage with surrounding erythema, edema, and/or induration which occurred within 30 days after the trauma or surgery and was associated with cellulitis such that:
- the total affected area involved at least 75 cm^2 of erythema, and
- was defined by a margin of erythema in at least 1 direction that was ≥5 cm from the edge of the wound, or
- alternatively, involved the central face and was associated with an affected area of at least 50 cm^2 and had a margin of erythema in at least 1 direction ≥3 cm from the wound edge.

c. Cellulitis, defined as a diffuse skin infection characterized by spreading areas of erythema, edema, and/or induration and
- was associated with erythema that involved at least 75 cm^2 of surface area, or
- alternatively, cellulitis of the central face that was associated with an affected area of at least 50 cm^2.

4. In addition to the requirement for erythema, all patients were required to have at least 2 of the following signs of ABSSSI:
- Purulent drainage/discharge
- Fluctuance
- Heat/localized warmth
- Tenderness to palpation
- Swelling/induration

5. Patients must have presented with ≥1 of the following systemic signs of infection:
- An elevated body temperature ≥ 38°C/100.4°F within 24 hours of Baseline
- White blood cell (WBC) count >12,000 cells/mm^3
- A manually performed WBC differential count with ≥10% band forms,
  - regardless of peripheral WBC count

6. Infection severity requiring a minimum of 3 days of IV therapy.
Patient was willing and able to comply with study procedures.

Exclusion Criteria:
The Reviewer's description of the Applicant's exclusion criteria is shown below:

1. Patients with a contraindication to the administration of dalbavancin, vancomycin, or linezolid.
2. Females of childbearing potential who were unable to take adequate contraceptive precautions, had a positive pregnancy result within 24 hours prior to study entry, were known to be pregnant, or were currently breastfeeding an infant.

3. Patients with sustained shock, defined as systolic blood pressure < 90 mm Hg for more than 2 hours despite adequate fluid resuscitation, with evidence of hypotension or need for sympathomimetic agents to maintain blood pressure.
4. Participation in another study of an investigational drug or device within 30 days before this trial began.
5. Receipt of a systemically or topically administered antibiotic with a gram-positive spectrum that achieved therapeutic concentrations in the serum or at the site of the ABSSSI within 14 days prior to randomization.
6. Infection due to an organism known prior to Study entry to be resistant to dalbavancin or vancomycin (vancomycin minimum inhibitory concentration [MIC] >8 μg/mL).
7. Patients with evidence of meningitis, necrotizing fasciitis, gas gangrene, gangrene, septic arthritis, osteomyelitis; endovascular infection.
8. Infections caused exclusively by gram-negative bacteria and infections caused by fungi, whether alone or in combination with a bacterial pathogen.
9. Venous catheter entry site infection.
10. Infections that involved diabetic foot ulceration, a perirectal abscess or a decubitus ulcer.
11. Patient with an infected device, even if the device was removed.
12. Gram-negative bacteremia, even in the presence of gram-positive infection or gram-positive bacteremia.
13. Patients whose ABSSSI was the result of having sustained full or partial thickness burns.
14. Patients with an infection involving a limb with evidence of critical ischemia of an affected limb.
15. Patients with ABSSSI such as superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that only required surgical drainage for cure.
16. Concomitant condition requiring any antibiotic therapy that would have interfered with the assessment of study drug for the condition under study.
17. Anticipated need of antibiotic therapy for longer than 14 days.
18. Patients who were placed in a hyperbaric chamber as adjunctive therapy for the ABSSSI.
19. More than 2 surgical interventions for the ABSSSI, or patients who were expected to require more than 2 such interventions.
20. Medical conditions in which chronic inflammation may have precluded assessment of clinical response to therapy even after successful treatment.
21. Absolute neutrophil count <500 cells/mm^3.
22. Known or suspected human immunodeficiency virus infected patients.
23. Patients with a recent bone marrow transplant (in post-transplant hospital stay).
24. Patients who were receiving oral steroids >20 mg prednisolone per day (or equivalent) or receiving immunosuppressant drugs after organ transplantation.
25. Patients who were receiving an antipyretic drug on a daily basis (whose regimen could not be modified during the first 3 days of study drug therapy.

26. Patients with a rapidly fatal illness, who were not expected to survive for 3 months.
27. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study.
28. Prior participation in Trial 301 or in Trial 302.

Randomization: A patient was eligible for randomization once it had been determined that he or she met all of the inclusion criteria and none of the exclusion criteria. Patients were to be randomly assigned in a 1:1 ratio to receive dalbavancin (2 doses given 1 week apart) and 10 to 14 days of placebo to vancomycin or 10 to 14 days of vancomycin/linezolid and 2 weekly doses of placebo to dalbavancin with stratification by presence or absence of fever at Baseline (a minimum of 40% of patients were to have fever at Baseline), geographic region, and infection type (cellulitis, major abscess [maximum of 30% of the total study population], and traumatic wound or surgical site infection) using block randomization (block size 4) via an Interactive Voice Randomization System (IVRS).

Analysis Populations: The analysis populations were defined as follows: (Reviewer analyses primarily considered the ITT population).

ITT population- All randomly assigned patients.

Safety Population- ITT patients who received at least 1 dose of dalbavancin or vancomycin (active) study drug.

MicroITT- ITT patients who had at least 1 gram-positive bacterial pathogen isolated at Baseline. The gram-positive bacterial pathogen must have been identified from a blood culture or from a culture of a microbiological sample obtained from the primary ABSSSI site from an acceptable source.

Clinically Evaluable Populations- Three CE populations were defined, the clinically evaluable at the end-of-treatment visit (CE-EOT), clinically evaluable at the short-term follow-up visit (CE-SFU), and clinically evaluable at the long-term follow-up visit (CE-LFU) populations. The CE population used in the analysis depended on the time point of the outcome measure being analyzed. The term "CE populations" was used to refer to all 3 of these CE populations. Key criteria regarding the inclusion/exclusion from the CE populations included the following:

- Patients had to adhere to protocol-defined inclusion/exclusion criteria (inclusion criteria 3, 4, 5, and 6 and exclusion criteria 5-16, 18-20, 23, and 24).
- Patient had to receive the correct study drug based on the randomization assignment
- Patients had to receive at least 1 dose (dalbavancin arm) or 50% of dosing (comparator arm).

- Site personnel involved in the assessment of efficacy parameters remained had to remain blinded to study treatment up to the time of the efficacy assessment.
- Patients could not have received >1 dose of any systemic concomitant antibiotic therapy (with the exception of systemic aztreonam, metronidazole, or oral vancomycin) which was potentially effective against the causative pathogen from the first dose of study drug until the EOT (CE-EOT population), the SFU (CE-SFU population), or the LFU (CE-LFU population) for non-ABSSSI indications.
- Meet clinical assessment criteria:
  - For the CE-EOT population- Completed the EOT assessments such that the patient could be defined as a clinical success or failure;
  - For the CE-SFU population- Completed the SFU assessments such that the patient could be defined as a clinical success or failure, unless the patient was considered a clinical failure at EOT;
  - For the CE-LFU population- Completed the investigator's assessment of response (i.e. was deemed either a continued success or a relapse/recurrence) at LFU;

ME population: All patients in both the MicroITT and CE-EOT populations.

Sample Size Determination: Sample size was determined based on the method of Farrington and Manning[6]. The sample size determination assumed a 1-sided alpha of 0.025, a 10% NI margin, 85% clinical response rate and 90% power. The 85% clinical response rate was based on a retrospective analysis in patients with cellulitis, major abscess, surgical or traumatic wound infection with a Baseline lesion area of ≥ 75 cm^2 included in VER001-9 Study (excluding missing data). A point estimate of 81% (293/362; 95% CI, 77% to 85%) of patients were clinical responders. The 85% clinical response estimate is based on the upper bound of this confidence interval.

Study Endpoints

Primary Efficacy Outcome Measure: The primary outcome measure was clinical response at 48-72 hours (± 3 hours, i.e., 45-75 hours) post study drug initiation.

Responders were defined according to the following criteria:

- The patient had no increase in lesion area at 48 to 72 hours after the first dose of Study drug therapy compared with the baseline measurement, and
- The patient had a temperature ≤ 37.6°C within 48 to 72 hours after the first dose of Study therapy followed by 2 additional temperature measurements ≤ 37.6°C separated by at least 3 hours and no more than 9 hours apart, and no intervening temperature >37.6°C (any method of temperature measurement).

Lesion area was defined as length × width, and lesion size was defined as length or width. The Baseline lesion measurement was defined as the measurement taken closest to but before the first dose of study drug. If multiple lesions measurements were taken within 48 to 72 hours after the first dose of study drug, the latest lesion measurement was used.
A patient was defined as a clinical non-responder based on the following criteria:

- The patient failed to meet the above responder criteria; or
- The patient died from any cause within the first 72 hours; or
- The patient initiated a new systemic antibacterial with gram-positive activity for the ABSSSI under study within the first 72 hours; or
- The patient had missing data at 48 to 72 hours for lesion size or temperature such that a clinical outcome could not be defined.

Secondary Efficacy Outcome Measure: The Applicant also pre-specified a secondary endpoint based on clinical status at EOT. The requirements for clinical success at EOT are shown below:

- The patient's lesion size, as defined by erythema, was decreased from Baseline;
- The patient's temperature was ≤ 37.6°C (by any measurement method);
- Local signs of fluctuance and localized heat/warmth were absent;
- Local signs of tenderness to palpation and swelling/induration were no worse than mild; and
- For patients with a wound infection, the severity of purulent drainage was improved and no worse than mild relative to Baseline.

Patients meeting any of the criteria below were classified as clinical failures:

- The patient failed to meet any of the above success criteria
- The patient received a new non-study systemic antibacterial treatment for the ABSSSI at any time from the first dose of study drug through the visit, or
- The patient died during the study period up to the visit, or
- Unless preplanned as part of nondrug therapy for the ABSSSI, the patient required surgical intervention more than 72 hours after the start of therapy for treatment of the ABSSSI under study, or
- The patient received study therapy for the ABSSSI under study beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy was needed for treatment of the underlying skin infection.

The Applicant also evaluated clinical status at SFU using the same criteria.

Other Outcome Measures: The Applicant also considered investigator assessment at EOT and SFU with success/failure criteria shown in **Table 4**.

Table 4: Investigator Assessment- Definition of Success/Failure

Success	Resolution or improvement of all signs and symptoms of the infection to such an extent that no further antibacterial treatment was given
Failure	Any of the following: • Persistence of ≥1 local or systemic signs and symptoms of ABSSSI such that new systemic antibacterial treatment was given • Unplanned surgical intervention >72 hours after start of therapy for the treatment of ABSSSI TEAE leading to discontinuation of study drug, and patient required additional antibiotic therapy to treat the ABSSSI • Received study therapy beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying skin infection • Death during the study period

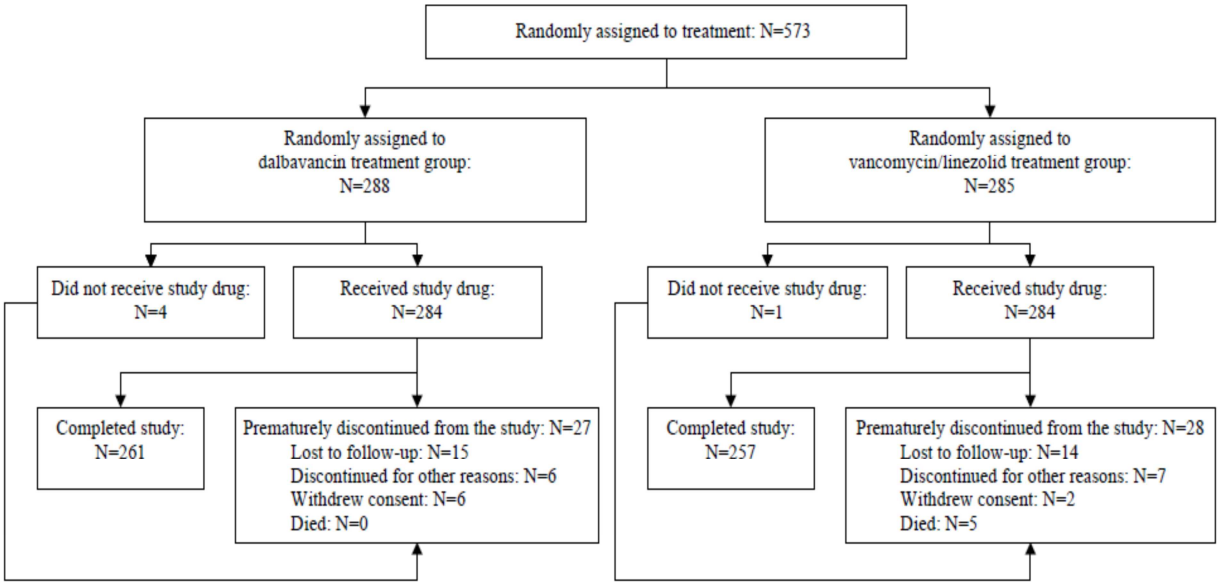
Source: Applicant Table 9.6 in Trial 301 CSR

3.2.2 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

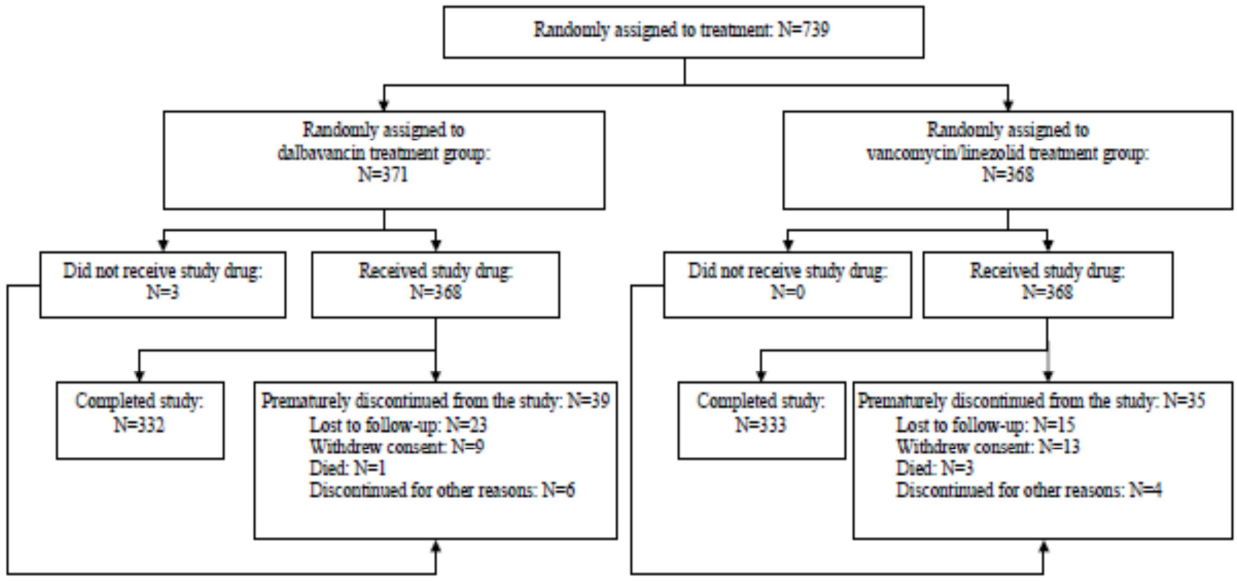
Subject disposition in Trials 301 and 302 is shown in the figures below. In Trial 301, there were 573 patients randomly assigned to treatment (288 patients and 285 patients in the dalbavancin and comparator groups), and 518 patients completed the study (261 patients and 257 patients in the dalbavancin and comparator groups). In Trial 302, 739 patients were randomly assigned to treatment (371 and 368 patients in the dalbavancin and comparator groups), and 665 patients completed the study (332 and 333 patients in the dalbavancin and comparator groups).

Figure 1: Trial 301- Subject Disposition (ITT)



Source: Partially Adapted from Applicant Figure 10.1 in Trial 301 CSR

Figure 2: Trial 302- Subject Disposition (ITT)



Source: Partially Adapted from Applicant Figure 10.1 in Trial 302 CSR

Table 5 shows the number (%) of patients by analysis populations in Trials 301 and 302. Overall, treatments were mostly similar with respect to the representation in each of the analysis populations. However, the dalbavancin arm included a slightly larger percentage of ITT patients in the micro and clinically evaluable populations. Comparing the combined treatment arms for Trial 301 vs. Trial 302, Trial 301 showed a larger percentage of ITT patients included in the MicroITT, ME and ME-SFU populations.

Table 5: Number (%) of Patients by Analysis Population, Trials 301 & 302

Analysis Population	Trial 301 (N=573)			Trial 302 (N=739)		
	Dalbavancin n (%)	Comparator n (%)	Total n (%)	Dalbavancin n (%)	Comparator n (%)	Total n (%)
ITT[1]	288 (100)	285 (100)	573 (100)	371 (100)	368 (100)	739 (100)
Safety	284 (99)	284 (100)	568 (99)	368 (99)	367 (100)	735 (99)
MicroITT	153 (53)	155 (54)	308 (54)	184 (50)	174 (47)	358 (48)
CE-EOT	246 (85)	243 (85)	489 (85)	324 (87)	302 (82)	626 (85)
CE-SFU	226 (78)	229 (80)	455 (79)	294 (79)	272 (74)	566 (77)
CE-LFU	219 (76)	212 (74)	431 (75)	280 (75)	267 (73)	547 (74)
ME	123 (43)	128 (45)	251 (44)	156 (42)	131 (36)	287 (39)
ME-SFU	110 (38)	118 (41)	228 (40)	143 (38)	120 (33)	263 (36)

[1]Primary analysis population was the ITT
Source: Reviewer Table

Demographic and Baseline Characteristics

In **Table 6**, demographic and baseline characteristics were generally similar between treatments (dalbavancin vs. comparator) in each of the two trials. In Trial 301, no substantial differences were noted between treatment arms. In Trial 302, more males (60.1% vs. 54.6%) and Hispanic/Latino subjects (17.0% vs. 12.2%) were enrolled in the dalbavancin arm. Comparisons of combined treatment arms (Trial 301 vs. Trial 302) showed Trial 301 as having more Hispanic/Latino patients (20.9% vs. 14.6%) and more patients from North America (42.6% vs. 31.0%).

Table 6: Demographics and Baseline Characteristics (ITT)

	Trial 301			Trial 302		
	Dalbavancin (N=288) n (%)	**Comparator (N=285) n (%)**	**Total (N=573) n (%)**	**Dalbavancin (N=371) n (%)**	**Comparator (N=368) n (%)**	**Total (N=739) n (%)**
Age						
Mean (Std. dev.)	48.8 (15.3)	48.9 (15.1)	48.9 (15.2)	49.1 (16.5)	51.4 (16.2)	50.2 (16.4)
Median (Min, Max)	50 (18, 84)	50 (18, 84)	50 (18, 84)	49 (18, 85)	51 (18, 84)	51 (18, 85)
Gender						
Male	170 (59.0)	173 (60.7)	343 (59.9)	223 (60.1)	201 (54.6)	424 (57.4)
Female	118 (41.0)	112 (39.3)	230 (40.1)	148 (39.9)	167 (45.4)	315 (42.6)
Ethnicity						
Hispanic/ Latino	59 (20.5)	61 (21.4)	120 (20.9)	63 (17.0)	45 (12.2)	108 (14.6)
Not Hispanic/ Latino	229 (79.5)	224 (78.6)	453 (79.1)	308 (83.0)	323 (87.8)	631 (85.4)
Race						
White	264 (91.7)	259 (90.9)	523 (91.3)	328 (88.4)	320 (87.0)	648 (87.8)
African American	16 (5.6)	19 (6.7)	35 (6.1)	13 (3.5)	17 (4.6)	30 (4.1)
Asian	1 (0.3)	2 (0.6)	3 (0.9)	27 (7.3)	30 (8.2)	57 (7.7)
Other	7 (2.4)	5 (1.8)	12 (2.1)	3 (0.8)	1 (0.3)	4 (0.5)
Region						
North America	123 (42.7)	121 (42.5)	244 (42.6)	115 (31.0)	114 (31.0)	229 (31.0)
Eastern Europe	165 (57.3)	164 (57.5)	329 (57.4)	225 (60.6)	223 (60.6)	448 (60.6)
Other	-	-	-	31 (8.4)	31 (8.4)	62 (8.4)
Infection Type						
Cellulitis	156 (54.2)	147 (51.6)	303 (52.9)	198 (53.4)	202 (54.9)	400 (54.1)
Major Abscess	72 (25.0)	86 (30.2)	158 (27.6)	91 (24.5)	87 (23.6)	177 (24.0)
Wound Infection	60 (20.8)	52 (18.2)	112 (19.5)	82 (22.1)	79 (21.5)	161 (21.8)

Source: Reviewer Table

Table 7 compares disease severity characteristics at baseline between treatments (dalbavancin vs. comparator) within each of the two trials. There were more dalbavancin patients with diabetes in Trial 301(14.9% vs. 10.5%) but fewer such patients in Trial 302 (9.4% vs. 16.8%). Comparing Trial 301 vs. Trial 302 (combined treatment arms), Trial 301 showed fewer patients over the age

of 65 (12.9% vs. 19.5%), fewer bacteremic patients (2.4% vs. 4.6%); and more patients with a prior surgical intervention (25.1% vs. 13.7%), severe erythema (68.3% vs. 49.2%), severe tenderness (64.5% vs. 55.7%) or severe swelling/induration (59.5% vs. 45.6%).

Table 7: Disease Severity at Baseline (ITT)

# (%) of subjects in categories below:	Trial 301			Trial 302		
	Dalbavancin (n=288)	**Comparator (n=285)**	**Total (n=573)**	**Dalbavancin (n=371)**	**Comparator (n=368)**	**Total (n=739)**
Risk Factors						
Age > 65 years	36 (12.5%)	38 (13.3)	74 (12.9)	68 (18.3)	76 (20.7)	144 (19.5)
Age > 75 years	14 (4.9)	14 (4.9)	28 (4.9)	30 (8.1)	28 (7.6)	58 (7.8)
Diabetes	43 (14.9)	30 (10.5)	73 (12.7)	35 (9.4)	62 (16.8)	97 (13.1)
Prior surgical intervention	69 (24.0)	75 (26.3)	144 (25.1)	53 (14.3)	48 (13.0)	101 (13.7)
Bacteremia	8 (2.8)	6 (2.1)	14 (2.4)	21 (5.7)	13 (3.5)	34 (4.6)
Renal function, CrCl	n=284	n=284	n=568	n=367	n=368	n=735
< 30 mL/min	11 (3.8)	8 (2.8)	19 (3.3)	9 (2.4)	7 (1.9)	16 (2.2)
≥ 30 mL/min	273 (96.1)	276 (97.2)	549 (96.7)	358 (97.5)	361 (98.1)	719 (97.8)
Systemic Signs						
Fever	236 (81.9)	235 (82.5)	471 (82.2)	303 (81.7)	303 (82.3)	606 (82.0)
Elevated WBC	n=259	n=254	n=513	n=368	n=367	n=735
Count > 12,000/mm^3	98 (37.8)	104 (40.9)	202 (39.4)	149 (40.5)	146 (39.8)	295 (40.1)
Local Signs						
Erythema	n=282	n=279	n=561	n=366	n=367	n=733
Absent	0	0	0	0	0	0
Mild	9 (3.2)	9 (3.2)	18 (3.2)	12 (3.3)	9 (2.5)	21 (2.9)
Moderate	82 (29.1)	78 (28.0)	160 (28.5)	176 (48.1)	175 (47.7)	351 (47.9)
Severe	191 (67.7)	192 (68.8)	383 (68.3)	178 (48.6)	183 (49.9)	361 (49.2)
Tenderness	n=282	n=279	n=561	n=366	n=367	n=733
Absent	1 (0.4)	3 (1.1)	4 (0.7)	0	2 (0.5)	2 (0.3)
Mild	16 (5.7)	9 (3.2)	25 (4.5)	14 (3.8)	22 (6.0)	36 (4.9)
Moderate	83 (29.4)	87 (31.2)	170 (30.3)	143 (39.1)	144 (39.2)	287 (39.2)
Severe	182 (64.5)	180 (64.5)	362 (64.5)	209 (57.1)	199 (54.2)	408 (55.7)
Swelling	n=282	n=279	n=561	n=366	n=367	n=733
Absent	0	0	0	3 (0.8)	1 (0.3)	4 (0.5)
Mild	22 (7.8)	16 (5.7)	38 (6.8)	21 (5.7)	17 (4.6)	38 (5.2)
Moderate	90 (31.9)	99 (35.5)	189 (33.7)	178 (48.6)	179 (48.8)	357 (48.7)
Severe	170 (60.3)	164 (58.8)	334 (59.5)	164 (44.8)	170 (46.3)	334 (45.6)

Source: Reviewer Table

Table 8 shows primary site infection site areas (cm^2) at baseline. Infection areas, both overall and by type of infection were generally larger in the comparator vs. the dalbavancin arm in both trials. Since infection area measurements were highly positively skewed, median area measurements were considered to be more informative for comparative purposes. Mean (median) infection areas for dalbavancin vs. comparator were 498 (333) vs. 533 (368) cm^2 in Trial 301 and 512 (314) vs. 580 (362) cm^2 in Trial 302. In Trial 301, there were substantial treatment differences in the median lesion area for subjects with cellulitis at 349 cm^2 vs. 496 cm^2. However, this difference was not significant based on the Wilcoxon rank sum test (p=0.174).

Table 8: Primary Infection Site: Area at Baseline, Overall and by Infection Type (ITT)

	Trial 301			Trial 302		
	Dalbavancin (n=288)	**Comparator (n=285)**	**Total (n=573)**	**Dalbavancin (n=371)**	**Comparator (n=368)**	**Total (n=739)**
Infection Area (cm^2), Overall						
n	284	284	568	368	368	736
Mean ± Std. dev.	498±505	533±512	515±508	512±558	580±594	546±577
Median (range)	333 (26, 3400)	368 (78, 3675)	351 (26, 3675)	314 (85, 5100)	362 (72, 3922)	336 (72, 5100)
Infection Area (cm^2), Subjects with Cellulitis						
n	154	146	300	197	202	399
Mean ± Std. dev.	614±630	671±588	642±610	675±691	722±688	699±689
Median (range)	349[1] (77,3400)	496[1] (81, 3675)	436 (77, 3675)	452 (85, 5100)	466 (72,3922)	462 (72,5100)
Infection Area (cm^2), Subjects with Major Abscesses						
n	70	86	156	90	87	177
Mean ± Std. dev.	351±247	329± 194	339±219	311±170	354±303	332±245
Median (range)	320 (26, 1390)	315 (88,1456)	315 (26,1456)	278 (110, 1008)	253 (80,1813)	266 (80, 813)
Infection Area (cm^2), Subjects with Traumatic wound/surgical site infection						
n	60	52	112	81	79	160
Mean ± Std. dev.	374 (217)	480 (528)	423±395	342±289	465±467	403±391
Median (range)	352 (84, 1383)	357 (78, 2820)	354 (78, 2820)	269 (88, 2006)	300 (90,2471)	286 (88,2471)

[1] Wilcoxon rank sum test for treatment difference showed a p-value = 0.174.

Source: Reviewer Table

3.2.3 Statistical Methodologies

Statistical Methodologies (Applicant)

The primary efficacy analysis was performed on the ITT population. The NI test was a 1-sided hypothesis test performed at the 2.5% level of significance and was based on the lower limit of the 2-sided 95% confidence interval (CI). The primary efficacy outcome measure was clinical response at 48 to 72 hours. The primary efficacy analysis was adjusted for the randomization stratification factor of presence or absence of fever at Baseline.

The number and percentage of patients in each treatment group defined as a clinical responder and non-responder were tabulated. The null and alternative hypotheses were as follows:

$H_0 : p_1 - p_2 \leq -\Delta$

$H_1 : p_1 - p_2 > -\Delta$

where p_1 was the rate of the primary efficacy outcome measure in the dalbavancin treatment group, p_2 was the rate of the primary efficacy outcome measure in vancomycin/linezolid treatment group, and Δ was the NI margin of 10%.

To test the null hypothesis, a 2-sided 95% CI for the observed difference in primary outcome rates (dalbavancin treatment group minus vancomycin/linezolid treatment group) was calculated. If the lower limit of the 95% CI for the treatment difference in the ITT population exceeded –10%, then the null hypothesis was rejected and the non-inferiority of dalbavancin to vancomycin/linezolid was concluded.

The 2-sided 95% CI for non-inferiority testing based on the difference of clinical response rates at 48-72 hours was computed using the method proposed with stratification by Miettinen and Nurminen[5] as described at the end of the Appendix.

NI Margin (Delta) Selection: A 10% non-inferiority margin was used to determine treatment efficacy in the primary analysis of Trials 301 and 302. A 10% NI margin is supported by findings from two historical studies (Snodgrass et. al, 1937)[3,4] comparing sulfonamides to UV light in patients diagnosed with erysipelas at the 48-72 hour time points.

Interim Analyses: In order to ensure that the point estimate of early clinical response used in the estimation of sample size was valid for this Study, an interim analysis for sample size re-estimation (SSR) was performed when early clinical response data at 48 to 72 hours were available for approximately 60% of the patients (334 patients). The interim analysis involved a SSR to either confirm the initial sample size estimate was adequate or increase the sample size to ensure the Study had adequate power for determining whether dalbavancin was non-inferior to vancomycin/linezolid for the primary outcome measure. The sample size re-estimation was based on the blinded overall (not by treatment group) clinical response rate and was conducted by an independent, blinded statistician. A Data Monitoring Committee (DMC) was provided with the results of the interim analysis by the independent, blinded statistician and made a recommendation regarding changes to the sample size.

Reviewer Comments: *The sample size was increased only in Trial 302 from an initially planned number of 556 subjects to approximately 740 subjects. This increase was based on the overall response rate observed at the interim analysis (i.e. 78.7%) which fell below the assumed rate of 85%. In order to maintain study power at 90%, the DMC recommended that the sample size be increased to 740 subjects. The actual number of ITT subjects in Trial 302 was 739.*

Missing Data: The Applicant notes the following regarding the handling of missing data in primary and secondary analyses.

- For the primary outcome measure (clinical response at 48 to 72 hours), the patient was considered to have missing data if there was no lesion measurement at Baseline and/or in the 48 to 72 hour (after first dose of study drug) time period. In addition, the patient was considered to have missing data if there were not 3 temperature measurements in the 48 to 72 hour time period taken 6 hours (±3 hours) apart. Patients with missing data were defined as a non-responder for the primary analysis (ITT analysis).
- For the secondary outcome measure (clinical status at EOT), patients were defined as an indeterminate if any data needed to determine whether a patient was a success or failure were missing. For example, if the assessment of the local signs was not completed at EOT, for any reason, the patient was considered an indeterminate response. By definition, patients with an indeterminate response were included in the denominator for analyses in the ITT and MicroITT populations, and were considered failures.
- For the investigator's assessment of clinical response at EOT and SFU, patients were considered an indeterminate response if data were not available for the evaluation of efficacy at EOT and SFU for any reason.
- For the investigator's assessment of clinical status at LFU, analysis of clinical status at LFU was only conducted in the CE-LFU population and in those patients who were a clinical success at EOT and SFU. Patients with missing data were excluded from the CE-LFU population and thus, were not included in the analysis.
- For microbiologic response, if no acceptable EOT source specimen was obtained and the patient had a clinical response assessment, the per-pathogen microbiological response was based on the clinical response assessment. A per-pathogen microbiological response at EOT was considered missing or indeterminate only if the clinical status at EOT was also missing or indeterminate.

A sensitivity analysis was completed for clinical status at EOT in the ITT population. Multiple imputation methods using a Markov chain Monte Carlo full data imputation was used to define missing data (i.e. patients with an indeterminate outcome). Two models were run, the first utilized type of infection as a predictive variable and the second utilized clinical response at 48 to 72 hours as a predictive variable.

Multiple Comparisons Adjustment: In the Applicant's primary hypotheses, only one statistical hypothesis was tested. All secondary and additional efficacy analyses were considered descriptive and supportive of the primary efficacy analysis. Therefore, no adjustments were made to control for inflation of the type I error rate.

Covariates: No adjustments for covariates were made to the primary analyses in the main analyses.

Statistical Methodologies (Reviewer)

The Reviewer also conducted the Applicant's primary analyses. Similar to the Applicant's primary analysis, responder rates in Reviewer analyses were evaluated using the lower 95% confidence limit of the treatment difference (dalbavancin minus comparator). Estimation of 95% confidence limits for the treatment difference in clinical response rates at 48-72 hours was also performed using the method proposed by Miettinen and Nurminen[5], adjusting for baseline fever status. Patients with missing data at the specified visit were generally considered as non-responders or failures.

To address both the Applicant's pre-specified primary endpoint and the primary endpoint recommended in the current ABSSI guidance[1], the Reviewer considered the former as the primary endpoint and the latter as a "key" secondary endpoint thought to play a pivotal role in determining overall efficacy. To further assess the robustness of findings during earlier time points, the Reviewer's analyses also compared the distributions of patients in each treatment arm meeting various other % reductions in lesion area at 48-72 hours.

After an evaluation of findings from earlier time points, the Reviewer then explored the question of whether the efficacy observed at 48-72 hours is consistent with that of later time points, such as at EOT on Day 14-15 and SFU on Day 26-30. To do this, the Reviewer's analyses primarily considered the clinical status at EOT (pre-specified secondary endpoint) and clinical status at SFU endpoints. However, these endpoints may not offer a clear interpretation since they did not allow for inferential testing due to uncertainty in the NI margin for later endpoints nor have any pre-specified 'win/lose' criteria. The clinical status endpoints also had other limitations in making efficacy comparisons. For example, these endpoints lacked appropriate success criteria relating to the required % reductions in lesion area and resolution of local signs (e.g. erythema).

Due to these limitations, the Reviewer conducted additional sensitivity analyses (referred to as S1-S4) which placed further requirements on success. In S1 & S2, clinical success at EOT required at least an 80% and 90% reduction in lesion size, respectively, along with an investigator rating for erythema of no worse than mild. In S3, clinical success at SFU required complete resolution (absence) of all local signs except for mild erythema if the lesion area is $\leq$ 10% of the baseline lesion area. In S4, clinical successes at SFU required complete resolution of all local signs. Local signs included purulent drainage/discharge, erythema, fluctuance, heat/warmth, tenderness to palpation, and swelling/induration. In addition to these sensitivity analyses, the Reviewer also performed concordance analyses to further explore the relationship between clinical response at 48-72 hours and clinical success (or complete resolution) at later visits.

These and other sensitivity analyses of interest are summarized below:

- Clinical Status at EOT Visit (ITT population) with stricter requirements for reductions in lesion area, such as 80% and 90% reduction in the ITT population (S1 & S2).
- Complete resolution of local signs at SFU with and without allowance of 10% residual erythema in the ITT population (S3 & S4).

- Success/resolution rates at EOT/SFU by responder status at 48-72 hours (concordance).
- Distributions of % reductions in erythema at 48-72 hours, EOT and SFU.
- Reasons for failure at 48-72 hours, EOT and SFU.
- Changes in individual local signs at EOT and SFU.
- Other analyses (e.g. clinical success rates at SFU by creatinine clearance at baseline, responder rates by NSAID use, etc.).

Reviewer Comments: *The analysis population considered was the ITT, unless otherwise stated. Confidence intervals displayed in the Reviewer tables for analyses of endpoints after 48-72 hours (e.g. EOT and SFU) generally used the Miettinen and Nurminen approach without adjustments.*

3.2.4 Results and Conclusions

Applicant's Analysis of Primary and Secondary Endpoints

Results of the primary analyses in Trial 301 and Trial 302 (as reported by the Applicant) are shown in **Table 9**. In this analysis, responder rates were compared between dalbavancin and the comparator at 48-72 hours using a 10% NI margin in the ITT population. Treatment differences were 1.5% (-4.6%, 7.9%) in Trial 301 and -1.5% (-7.4%, 4.6%) in Trial 302. Since the lower limits of the 95% confidence intervals for the treatment differences in both trials were above -10% (i.e. at -7.4% or greater), these findings supported the Applicant's objective of demonstrating non-inferiority of dalbavancin to the comparator based on the clinical responder rate at 48-72 hours.

Table 9: Responder Rates at 48-72 hours: Applicant Primary Analysis (ITT)

Trial 301			Trial 302		
Dalbavancin (n=288) n (%)	Comparator (n=285) n (%)	Dalbavancin − Comparator (95% CI)[1]	Dalbavancin (n=371) n (%)	Comparator (n=368) n (%)	Dalbavancin − Comparator (95% CI)[1]
240 (83.3)	233 (81.8)	1.5 (-4.6, 7.9)	285 (76.8)	288 (78.3)	-1.5 (-7.4, 4.6)

[1] 95% CIs were calculated using the Miettinen and Nurminen approach, adjusted for baseline fever status.
Responders require cessation of spread of lesion and absence of fever at 48-72 hours AND could not use new non-study systemic antibiotics or have a death in the study period up to 48-72 hours.
Source: Reviewer Table

Results of the Applicant's analysis of the pre-specified secondary endpoint of clinical status at EOT in Trials 301 and 302 are shown in **Table 10**. In Trial 301, Applicant findings in the ITT population were less favorable in the dalbavancin arm with a treatment difference in success rates of -4.8% (-10.7%, 1.3%). In contrast, Applicant findings in Trial 302 favored dalbavancin at 3.1% (-1.8%, 8.0%). However, it is important to note that the Agency cannot interpret non-inferiority comparisons at later endpoints due to the lack of available data in the literature supporting a NI margin at visits occurring after 72 hours (e.g. EOT, SFU visits).

Reviewer Comments: *The Agency also considers NI comparisons in the ITT population to be more interpretable as this population is protected by randomization.*

Table 10: Success Rates for Clinical Status at EOT, Applicant Analyses

Trial 301			Trial 302		
Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)
ITT Population					
236/288 (81.9)	247/285 (86.7)	-4.8 (-10.7, 1.3)	329/371 (88.7)	315/368 (85.6)	3.1 (-1.8, 8.0)
CE-EOT Population					
214/246 (87.0)	222/243 (91.4)	-4.4 (-10.0, 1.2)	303/324 (93.5)	280/302 (92.7)	0.8 (-3.3, 5.0)

[1] 95% CIs were calculated using the Miettinen and Nurminen approach, adjusted for fever status at baseline.
Source: Reviewer Table

Reviewer Comments: *The Applicant also evaluated success rates based on investigator assessment at EOT & SFU. Findings from these analyses are shown in the Appendix, Table* **Table 30**.

Reviewer Analyses of Primary and Key Secondary Endpoints

In **Table 11**, responder rates for cessation of spread of lesion and absence of fever were the same as those of the Applicant at 83.3% vs. 81.8%, 1.5% (-4.6%, 7.9%) in Trial 301 and 76.8% vs. 78.3%, -1.5% (-7.4%, 4.6%) in Trial 302. Responder rates based on at least a 20% reduction in lesion size at 48-72 hours (with no fever component) were 89.9% vs. 90.9%, -1.0% (-5.7%, 4.0%) in Trial 301 and 87.6% vs. 85.9%, 1.7% (-3.2%, 6.7%) in Trial 302. These results further supported the non-inferiority of dalbavancin to the comparator at 48-72 hours from baseline since the lower limit of the 95% CI for the treatment difference was at or above -7.4% (i.e. greater than -10%) in all analyses below.

Table 11: Reviewer Analyses: Responder Rates at 48-72 hours (ITT)

	Trial 301			Trial 302		
Responder Rates:	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)[1]	Comparator (N=371) n (%)	Dalbavancin (N=368) n (%)	Difference (95% CI)[1]
Primary Cessation of spread & afebrile at 48-72 hrs	240 (83.3)	233 (81.8)	1.5 (-4.6, 7.9)	285 (76.8)	288 (78.3)	-1.5 (-7.4, 4.6)
Key Secondary ≥ 20% reduction in lesion area at 48-72 hrs	259 (89.9)	259 (90.9)	-1.0 (-5.7, 4.0)	325 (87.6)	316 (85.9)	1.7 (-3.2, 6.7)

	Trial 301			Trial 302		
Responder Rates:	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)[1]	Comparator (N=371) n (%)	Dalbavancin (N=368) n (%)	Difference (95% CI)[1]
Primary Cessation of spread & afebrile at 48-72 hrs	240 (83.3)	233 (81.8)	1.5 (-4.6, 7.9)	285 (76.8)	288 (78.3)	-1.5 (-7.4, 4.6)

[1] 95% CIs were calculated using the Miettinen and Nurminen approach, adjusted for baseline fever status. Responders also could not use new non-study systemic antibiotics or have a death in the study period up to 48-72 hours.

Source: Reviewer Table

Reviewer Comment: *In the table above, there were 7 patients who did not receive any treatment and were counted as nonresponders (3 dalbavancin patients in Trial 301; 3 dalbavancin patients and 1 comparator patient in Trial 302). Error! Reference source not found.*

Reviewer Analyses of Later Endpoints (EOT & SFU)

In **Table 12**, the Reviewer's analyses of later endpoints considered the Applicant's pre-specified secondary endpoint of clinical status at EOT and the endpoint of clinical status at SFU. These analyses address the consistency of the clinical response achieved at 48-72 hours with the response at later time points. In Trial 301, the response rates at these later endpoints were lower in the dalbavancin than in the comparator arm. In the ITT population, comparisons of success rates were 81.3% vs. 86.7%, -5.4% (-11.5, 0.6) at EOT and 83.7% vs. 88.1%, -4.4% (-10.2, 1.3) at SFU. In contrast, Trial 302 comparisons favored the dalbavancin arm at 88.7% vs. 85.3%, 3.4% (-1.5, 8.3) for EOT and 88.1% vs. 84.5%, 3.6% (-1.3, 8.7) for SFU.

Table 12 also shows a high degree of variability in success rates across trials. Reasons for this are not clear but may be influenced by trends in the rates of indeterminate/missing outcomes at EOT and SFU which were classified as failures. For example, Trial 301 rates of missing or indeterminate outcomes at EOT were higher in the dalbavancin vs. the comparator arm at 14/288 (4.9%) vs. 9/285 (3.2%), a difference of 1.7%, while Trial 302 rates were lower in the dalbavancin arm at 10/371 (2.7%) vs. 20/368 (5.4%), a difference of -2.7%. Due to these trends, true clinical failure rates (excluding the indeterminates) were less pronounced and fairly modest at EOT and SFU with the exception of Trial 301 at the EOT assessment where the difference was 3.7%.

Reviewer Comments: *The table below shows success rates in the ITT population. Corresponding rates in the CE-EOT or CE-SFU populations are provided in the Appendix **Table 36**. As previously noted, this Review primarily considers the ITT population. Analyses in the ITT population have the advantage that patients are protected by the initial randomization. The randomization can also be stratified to balance treatments with respect to confounding factors (e.g. stratification by baseline fever status, infection type and geographic region in Trials 301 and 302). In contrast, analyses in the CE-EOT and CE-SFU populations make post-randomization exclusions in which the remaining subgroup of patients analyzed would not have randomization protection. This can lead to treatment imbalances with respect to important confounding factors.*

Table 12: Reviewer Analyses of Clinical Status, Success Rates at EOT & SFU (ITT)

Clinical Status at EOT[2] and SFU Outcome	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)[1]
Trial 301	N=288	N=285	
Success, EOT	**234 (81.3%)**	**247 (86.7%)**	**-5.4% (-11.5, 0.6)**
Failure	40 (13.9)	29 (10.2)	3.7
Indeterminate	14 (4.9)	9 (3.2)	1.7
Success, SFU	**241 (83.7%)**	**251 (88.1%)**	**-4.4% (-10.2, 1.3)**
Failure	18 (6.3)	13 (4.6)	1.7
Indeterminate	29 (10.1)	21 (7.4)	2.7
Trial 302	N=371	N=368	
Success, EOT	**329 (88.7%)**	**314 (85.3%)**	**3.4% (-1.5, 8.3)**
Failure	32 (8.6)	34 (9.2)	-0.6
Indeterminate	10 (2.7)	20 (5.4)	-2.7
Success, SFU	**327 (88.1%)**	**311 (84.5%)**	**3.6% (-1.3, 8.7)**
Failure	18 (4.9)	23 (6.3)	-1.4
Indeterminate	26 (7.0)	34 (9.2)	-2.2

[1] 95% CIs were calculated using the Miettinen and Nurminen approach, unadjusted.
[2] Clinical status at EOT was a pre-specified secondary endpoint.
Source: Reviewer Table

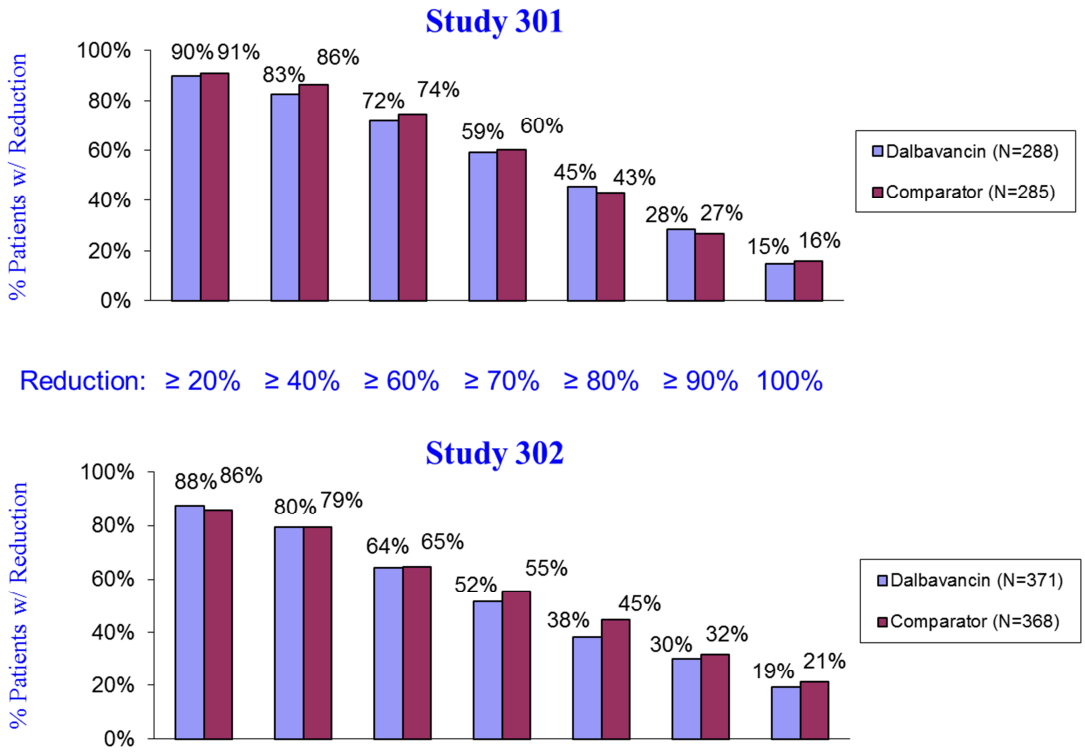
Reviewer Comments: *Rates of clinical success at EOT in the ITT population in the Reviewer analysis differ slightly from those reported by the Applicant in* **Table 10**. *The Applicant's analyses only require that successes have a decrease in lesion area at EOT, while the Reviewer analyses require that successes have a decrease in 'lesion size' where 'lesion size' is defined in the protocol (as well as the efficacy datasets) as a decrease in both length and width dimensions. In contrast to Applicant analyses, Reviewer analyses classified two dalbavancin patients in Trial 301 and one comparator patient in Trial 302 as failures. These patients had a decrease in lesion 'area' but not lesion 'size' (i.e. length and width).*

Reviewer Sensitivity Analyses at 48-72 hours

To further assess the robustness of findings obtained from the endpoints assessing efficacy at 48-72 hours, the Reviewer conducted a sensitivity analysis which considered the distribution of patients in each treatment arm meeting various % reductions in lesion area at 48-72 hours (**Figure 3**). In addition to considering responders based on meeting a 20% reduction in lesion area, these analyses also considered responders based on meeting 40%, 60%, 70%, 80%, 90% and 100% reductions. Findings from this analysis show the comparator being more favorable for most of

the % reduction categories. However, since treatment differences were generally small, these results were viewed as being further supportive of the non-inferiority of dalbavancin to the comparator at 48-72 hours.

Figure 3: Distribution of Patients Meeting Various % Reductions in Lesion Area at 48 -72 hours



Patients meeting % reductions could not have a death, use non-study antibacterials or have an unplanned surgical intervention (if more than 72 hours after start of study therapy) up to the EOT/SFU visit.
Source: Reviewer Figure

Reviewer Sensitivity Analyses at EOT & SFU

The Reviewer considered the analyses of clinical status at EOT and at SFU as having a major limitation in that the success criteria, as defined by the Applicant, did not have strict enough requirements placed on certain signs/symptoms. For the local sign of erythema, patients needed to only show a decrease in lesion size at EOT and SFU (i.e. any magnitude of decrease). However, such a requirement is not consistent with the requirements for responders in the key secondary endpoint (i.e. at least a 20% reduction in lesion area at 48-72 hours), especially when taking into account the progression towards resolution of erythema expected by the EOT and SFU visits on Day 14-15 and Day 26-30, respectively.

Consequently, sensitivity analyses for these endpoints were conducted using stricter requirements for the lesion area/erythema at EOT. Sensitivity analyses S1 & S2 have the additional requirement that the % reduction in lesion area is 80% & 90% respectively and the erythema rating is no worse than mild. Additional sensitivity analyses (S3 & S4) considered the SFU visit in which success was defined as complete resolution (absence) of all local signs except for mild residual erythema if the lesion area was no greater than 10% of the area at baseline (S3) and complete resolution of all local signs (S4). The local signs included purulent drainage/discharge, erythema, fluctuance, heat/warmth, swelling/induration and tenderness to palpation. The systemic component of fever was not included in these outcomes due to a substantial number of patients who were missing fever measurements at EOT and SFU.

Reviewer Comments: *Reviewer sensitivity analyses such as S1-S4 are post-hoc analyses and were conducted for the purpose of exploration.*

Table 13 shows the findings from sensitivity analyses S1-S4 (clinical status is also shown for comparison). In Trial 301, success rates for clinical status and S1-S4 were unfavorable for dalbavancin with upper 95% confidence limits for the treatment difference near or below 0. In contrast, success rates in Trial 302 favored dalbavancin over the comparator for clinical status and S1-S4 with a lower 95% confidence limit of -5% or greater. S1-S4 also show that success rates at EOT and SFU become less favorable in Trial 301 and more similar in Trial 302 as stricter requirements for success are placed on % reductions in lesion area/erythema and other local signs.

Table 13: Sensitivity Analyses of Later Endpoints in Trials 301 and 302 (ITT)

Endpoint Definition	**Dalbavancin n/N (%)**	**Comparator n/N (%)**	**Difference (95% CI)**
Trial 301	N=288	N=285	
Clinical Status, EOT	**234 (81.3%)**	**247 (86.7%)**	**-5.4% (-11.5, 0.6)**
S1	226 (78.5)	242 (84.9)	-6.4 (-12.8, -0.1)
S2	218 (75.7)	237 (83.2)	-7.5 (-14.1, -0.8)
Clinical Status, SFU	**241 (83.7%)**	**251 (88.1)**	**-4.4 (-10.2, 1.3)**
S3	229 (79.5)	241 (85)	-5.1 (-11.4, 1.3)
S4	220 (76.4)	239 (84)	-7.5 (-14.0, -0.9)
Trial 302	N=371	N=368	
Clinical Status, EOT	**329 (88.7%)**	**314 (85.3%)**	**3.4% (-1.5, 8.3)**
S1	318 (85.7)	306 (83.2)	2.6 (-2.7, 7.8)
S2	309 (83.3)	299 (81.3)	2.0 (-3.5, 7.6)
Clinical Status, SFU	**327 (88.1)**	**311 (84.5)**	**3.6 (-1.3, 8.7)**

Table 13: Sensitivity Analyses of Later Endpoints in Trials 301 and 302 (ITT)

Endpoint Definition	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)
S3	298 (80.3)	288 (78.3)	2.1 (-3.8, 7.9)
S4	292 (78.7)	286 (77.7)	1.0 (-5.0, 7.0)

Source: Reviewer Table

Reviewer sensitivity analyses also considered the most common reasons for failure in the clinical status at EOT/SFU endpoints, as shown in **Table 14**. In this table, two sets of numbers are shown. The first set is the number of failures due to the reason (other reasons possible) and the second set (in parentheses) is the number of failures due to the reason only (no other reasons). If a relatively large number of failures are due to a given reason only then may that reason unduly influence the clinical status endpoint. **Table 14** shows that the presence of heat/warmth appears to be unduly influencing the clinical status endpoint, especially in Trial 301 where there were 30 patients (19 dalbavancin and 11 comparator) who failed only due to heat/warmth. This is substantially higher than the next most influential reason (i.e. lesion size not decreased) where 3 patients (2 dalbavancin and 1 comparator) had failed only because of that reason. At SFU, however, non-study systemic antibiotic use was the most influential reason for failure in both trials. There were more patients in the dalbavancin arm failing only due to this reason in Trial 301 (9 vs. 3 failures) compared to the next most influential reason of heat/warmth being present.

Table 14: Clinical Status at EOT/SFU: Reasons for Failure (ITT)

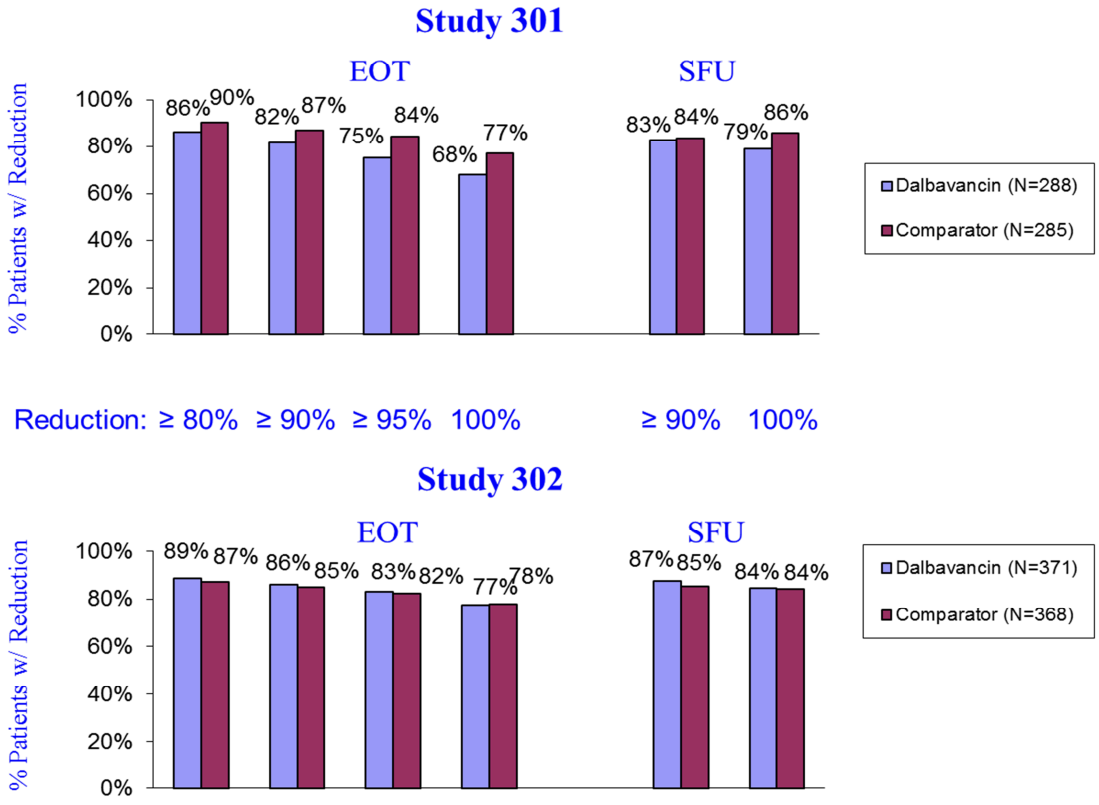
	Trial 301		Trial 302	
	Dalbavancin N=288	**Comparator N=285**	**Dalbavancin N=371**	**Comparator N=368**
# Failures due to reason (# Failures due to reason ONLY)				
Clinical Failures, EOT	**n=40**	**n=29**	**n=32**	**n=34**
Heat/warmth present	31 (19)	21 (11)	16 (5)	20 (6)
Non-study systemic abx	13 (1)	4 (0)	9 (1)	14 (0)
Lesion size not decreased	10 (2)	3 (1)	7 (1)	5 (2)
Swelling worse than mild	6 (1)	6 (1)	8 (2)	13 (2)
Clinical Failures, SFU	**n=18**	**n=13**	**n=18**	**n=23**
Non-study systemic abx	16 (9)	7 (3)	11 (7)	15 (8)
Heat/warmth present	5 (2)	2 (0)	1 (1)	3 (1)

Source: Reviewer Table

Reviewer Comments: *Reasons and timing of non-study systemic antibacterial use through SFU are shown in the Appendix,* **Table 36***.Error! Reference source not found.*

In **Figure 4,** Reviewer sensitivity analyses also considered the distribution of patients in each treatment arm meeting various % reductions in lesion area at EOT and SFU. In Trial 301, patients in the dalbavancin arm had substantially lower responder rates when requiring responders to have 80%, 90%, 95% and 100% reductions at EOT or 90% and 100% reductions at SFU. Findings from Trial 301 also show a trend towards less favorable treatment differences for dalbavancin when requiring responders to have larger % reductions at EOT and SFU. However, similar trends were not observed in Trial 302, even when requiring the largest % reductions at EOT and SFU.

Figure 4: Distribution of Patients Meeting Various % Reductions in Lesion Area at EOT and SFU



Patients meeting % reductions could not have a death, use non-study antibacterials or have an unplanned surgical intervention (if more than 72 hours after start of study therapy) up to the EOT/SFU visit.
Source: Reviewer Figure

Reviewer Comments: *In Trial 301, findings for 100% reduction in lesion size at EOT and SFU indicate that more patients in the comparator arm are achieving larger % reductions and are having a faster progression towards complete resolution of erythema. However, similar findings were not observed in Trial 302.*

Additional Reviewer sensitivity analyses (or concordance analyses) explored the relationship between early and later endpoints. Findings showed dalbavancin as being less favorable vs. the comparator in patients who are early responders. For example, concordance analyses of early clinical response (responder/non-responder) and resolution of local signs (complete/incomplete) showed a substantially smaller percentage of early responders achieving complete resolution at SFU in the dalbavancin arm vs. the comparator arm. As shown in the Appendix, **Table 25,** the success (complete resolution) rate was 80.8% vs. 88.8%, -8.0% (-14.5, -1.6) in Trial 301 and 82.5% vs. 84.0%, -1.6% (-7.8, 4.6) in Trial 302. Note that these findings were less favorable than those of corresponding analyses that included both responders and non-responders where treatment differences for success rates were -7.5% (-14.0, -0.9) in Trial 301 and 1.0% (-5.0, 7.0) in Trial 302, **Table 13**. Refer to Section 4.2 for further discussion of concordance analyses.

Conclusions

Trials 301 & 302 both met their primary and key secondary endpoints at 48-72 hours. Although overall findings appeared to be robust at 48-72 hours, there is still uncertainty at the later time points due to unfavorable findings from Trial 301. This uncertainty was evidenced in the analyses of the clinical status endpoints and especially in the sensitivity analyses and concordance analyses. These analyses also show a trend towards less favorable findings when placing stricter criteria on the resolution of erythema (e.g. % reductions in lesion size).

3.3 Evaluation of Safety

According to the Clinical Reviewer, Dr. Dmitri Iarikov, dalbavancin demonstrated an overall favorable safety profile with similar rates of mortality and non-fatal adverse events as the comparators. The major safety finding reported was possible dalbavancin-associated liver injury, especially in subjects with underlying liver disease. This finding is based on an observation of several cases of high-degree transaminase enzyme elevations in dalbavancin-treated subjects which were not observed in the comparator group. Another safety finding is a higher rate of adverse events related to hemorrhages in dalbavancin-treated subjects, including gastrointestinal and soft-tissue hemorrhages. Refer to Dr. Iarikov's Review for further details regarding safety.

While safety is not the primary focus of this Review, **Table 15** shows the reasons for patient discontinuations in Trials 301 & 302 (combined). These findings did not show large treatment differences in any of the categories.

Table 15: Study Drug Discontinuation (Trials 301 & 302 Combined, ITT)

Reason for Discontinuation	Dalbavancin N (%)	Comparator N (%)
Randomized (ITT)	659 (100)	653 (100)
Received study drug	652 (98.9)	651 (99.7)
Study drug discontinued	44 (6.7)	51 (7.8)
Adverse event	11 (1.7)	14 (2.1)

Reason for Discontinuation	Dalbavancin N (%)	Comparator N (%)
Lack of efficacy	8 (1.2)	8 (1.2)
Withdrawal by subject	6 (0.9)	9 (1.4)
Subject non-compliance	3 (0.5)	0 (0)
Other	16 (2.4)	20 (3.1)

Source: Partially Adapted from Table 14 in Summary of Clinical Efficacy

4. SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analyses by Age, Gender, Race and Geographic Region

Table 16 shows clinical response rates at 48-72 hours by subgroups based on age (< 65 yrs vs. ≥ 65 yrs), gender (male vs. female), race (white vs. non-white) and geographic region (North America vs. all other regions). There were no notable trends consistently favoring either treatment arm across both trials. In Trial 301, dalbavancin patients who were female or from North America fared slightly better vs. the comparator in Trial 301, however, similar trends were not observed in Trial 302. For the variable of region, clinical response rates were observed to be lower in North America vs. all other regions in Trial 301 but substantially higher in Trial 302. Note, however, that analyses in the ≥ 65 years of age and the non-white subgroups were limited by small numbers.

Table 16: Responder Rates at 48-72 hours by Age, Gender, Race and Region (ITT)

Variable / Subgroup	Trial 301 (n=573)			Trial 302 (n=739)		
	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI))	Dalbavancin (N=371) n (%)	Comparator (N=368) n (%)	Difference (95% CI)
Age						
< 65	208/251 (82.9)	200/242 (82.6)	0.2 (-6.5, 7.0)	228/301 (75.7)	222/287 (77.4)	-1.6 (-8.5, 5.3)
≥ 65	32/37 (86.5)	33/43 (76.7)	9.7 (-8.1, 26.8)	57/70 (81.4)	66/81 (81.5)	-0.1 (-13.0, 12.4)
Gender						
Male	140/170 (82.4)	145/173 (83.8)	-1.5 (-9.5, 6.6)	174/223 (78.0)	160/201 (79.6)	-1.6 (-9.4, 6.3)
Female	100/118 (84.8)	88/112 (78.6)	6.2 (-3.9, 16.4)	111/148 (75.0)	128/167 (76.7)	-1.7 (-11.2, 7.8)
Race						
White	222/264 (84.1)	215/259 (83.0)	1.1 (-5.3, 7.5)	255/328 (77.7)	252/320 (78.8)	-1.0 (-7.4, 5.4)
Nonwhite	18/24 (75.0)	18/26 (69.2)	5.8 (-19.6, 30.1)	30/43 (69.8)	36/48 (75.0)	-5.2 (-23.7, 13.2)

Variable / Subgroup	Trial 301 (n=573)			Trial 302 (n=739)		
	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI))	Dalbavancin (N=371) n (%)	Comparator (N=368) n (%)	Difference (95% CI)
Geographic Region						
North America	100/123 (81.3)	93/121 (76.9)	4.4 (-5.9, 14.7)	96/115 (83.5)	96/114 (84.2)	-0.7 (-10.5, 9.0)
All other regions	140/165 (84.8)	140/164 (85.4)	-0.6 (-8.4, 7.3)	189/256 (73.8)	192/254 (75.6)	-1.8 (-9.3, 5.8)

Source: Reviewer Table

Reviewer Comments*: The table above is repeated with responders defined by a ≥ 20% reduction in lesion area in the Appendix,* ***Table 28****.*

4.2 Other Special/Subgroup Populations

Analyses of Primary Endpoint by Other Variables

Table 17 shows analyses of clinical response rates at 48-72 hours by other variables. For the fever status variable, clinical response rates were higher among patients with fever at baseline for both trials. In patients who were afebrile at baseline (approx. 18% of patients in each trial), treatment differences favored dalbavancin in Trial 301 and the comparator in Trial 302. For infection type, Trial 302 showed higher response rates among subjects with major abscesses vs. other infection types. It is not clear how much the incision and drainage procedure may have influenced the treatment effect in this trial. Although there were some treatment differences in individual trials (e.g. Trial 301 favored dalbavancin for cellulitis and Trial 302 favored the comparator for major abscesses), such findings were not consistent across both trials. For prior use of NSAIDs, responder rates in dalbavancin patients receiving NSAIDS within 3 days of the initiation of study therapy were substantially lower than in patients not receiving NSAIDs, although sample sizes were small. Study differences were also noted in the responder rates of patients receiving vs. not receiving IV therapy within first 72 hours as an inpatient, being substantially higher among those receiving IV therapy in Trial 301 and substantially lower among those receiving IV therapy in Trial 302.

Table 17: Clinical Response Rates at 48-72 hours by Other Variables (ITT)

Subgroup Variable Category	Trial 301 (n=573)			Trial 302 (n=739)		
	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)	Dalbavancin (N=371) n (%)	Comparator (N=368) n (%)	Difference (95% CI)
Fever Status						
Febrile	200/236 (84.7)	200/235 (85.1)	-0.4 (-6.9. 6.2)	239/303 (78.9)	237/303 (78.2)	0.7 (-5.9, 7.2)
Afebrile	40/52 (76.9)	33/50 (66.0)	10.9 (-6.7, 28.2)	46/68 (67.6)	51/65 (78.5)	-10.9 (-25.6, 4.4)
Infection Type						
Cellulitis	133/156 (85.3)	116/147 (78.9)	6.4 (-2.3, 15.1)	148/198 (74.7)	153/202 (75.7)	-1.0 (-9.5, 7.5)
Major Abscess	58/72 (80.6)	73/86 (84.9)	-4.3 (-16.8, 7.5)	75/91 (82.4)	76/87 (87.4)	-4.9 (-15.7, 5.9)
Wound Infection	49/60 (81.7)	44/52 (84.6)	-2.9 (-17.0, 11.7)	62/82 (75.6)	59/79 (74.7)	0.9 (-12.5, 14.4)
Received Antipyretic in 3 days prior to first dose of study drug						
Yes	51/59 (86.4)	43/52 (82.7)	3.8 (-10.0, 18.1)	60/88 (68.2)	78/104 (75.0)	-6.8 (-19.7, 5.9)
No	189/229 (82.5)	190/233 (81.5)	1.0 (-6.1, 8.0)	225/283 (79.5)	210/264 (79.5)	0.0 (-6.8, 6.8)
Received an NSAID in 3 days prior to first dose of study drug						
Yes	40/46 (87.0)	47/52 (90.4)	-3.4 (-17.5, 9.8)	24/33 (72.7)	34/39 (87.2)	-14.5 (-33.6, 4.1)
No	200/242 (82.6)	186/233 (79.8)	2.8 (-4.4, 9.8)	261/338 (77.2)	254/329 (77.2)	0.0 (-6.4, 6.4)
Received IV therapy within first 72 hours as an inpatient						
Yes	149/173 (86.1)	152/177 (85.9)	0.3 (-7.2, 7.7)	179/242 (74.0)	188/249 (75.5)	-1.5 (-9.2, 6.2)
No	91/115 (79.1)	81/108 (75.0)	4.1 (-7.0, 15.3)	106/129 (82.2)	100/119 (84.0)	-1.9 (-11.3, 7.7)
Enrolled Prior to or After Interim Analysis (Trial 302 only)						
Prior to	-	-	-	129/166 (77.7)	133/168 (79.2)	-1.5 (-10.3, 7.4)
After	-	-	-	156/205 (76.1)	155/200 (77.5)	-1.4 (-9.6, 6.9)

Source: Reviewer Table

Analyses of Primary Endpoint by Baseline Pathogen

Analyses of the primary endpoint by major pathogen from the primary infection site in the micro-ITT population are presented in **Table 18**. In both trials, clinical response rates at 48-72 hours tended to be lower in the dalbavancin vs. the comparator arm for S. *aureus* and MSSA pathogens.

Table 18: Responder Rates at 48-72 hours by Baseline Pathogen (MicroITT)

	Trial 301		Trial 302	
	Dalbavancin (N=153)	**Comparator (N=155)**	**Dalbavancin (N=184)**	**Comparator (N=174)**
S.aureus	103/122 (84.4%)	112/128 (87.5%)	103/135 (76.3%)	107/128 (83.6%)
MRSA	37/44 (84.1)	32/39 (82.1)	35/46 (76.1)	24/28 (85.7)
MSSA	66/78 (84.6)	79/88 (89.8)	68/89 (76.4)	84/101 (83.2)
S. agalactiae	2/3 (66.7)	5/6 (83.3)	4/9 (44.4)	6/8 (75.0)
S.anginosus[1]	4/7 (57.1)	12/13 (92.3)	14/15 (93.3)	11/12 (91.7)
S.pyogenes	10/12 (83.3)	8/14 (57.1)	18/25 (72.0)	16/22 (72.7)

[1] Refers to the *S.anginosus* group which includes *S. anginosus*, *S.intermedius*, and *S. constellatus.*
Source: Reviewer Table

Analyses of Other Exploratory Subgroups

Patients with Concomitant NSAID Use: Analyses explored the relationship between the duration of concomitant NSAID use after initiation of study therapy and clinical response at 48-72 hours (responder rates), as shown in **Table 19**. NSAID use closer in proximity to the assessment of early clinical response is more likely to confound the effect of the study drug on clinical response. To explore whether the duration of NSAID use could favor a particular treatment arm, three categories were used to classify patient NSAID use. That is, NSAID use within the first 24 hours, NSAID use within the first 48 hours and NSAID use within the first 72 hours after the initiation of study therapy. Note that patients with NSAID after 48 hours would be represented in all 3 categories.

In the combined treatment arms of Trials 301 & 302, there were 124 (22%) & 83 (11%) of patients with concomitant anti-inflammatory use in the first 72 hours following the start of study therapy. However, it is not clear as to whether the dalbavancin arm would have substantially benefitted from such confounding. Although numbers were small, the inclusion of patients receiving NSAIDs between 48 and 72 hours (where confounding is most likely to occur) tended to result in less favorable treatment differences for dalbavancin patients.

Table 19: Clinical Response at 48-72 Hours by Concomitant NSAID Use (ITT)

Duration of NSAID use after start of therapy	Trial 301 (n=573)			Trial 302 (n=739)		
	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)	Dalbavancin (N=368) n (%)	Comparator (N=371) n (%)	Difference (95% CI)
≤ 24 hours	10/12 (83.3)	9/13 (69.2)	14.1 (-21.2, 46.1)	11/16 (68.8)	8/11 (72.7)	-4.0 (-36.5, 32.2)

≤ 48 hours	24/27 (88.9)	20/25 (80.0)	8.9 (-11.8, 30.3)	17/23 (73.9)	13/17 (76.5)	-2.6 (-28.7, 26.0)
≤ 72 hours	51/58 (87.9)	59/66 (89.4)	-1.5 (-13.8,10.2)	33/45 (73.3)	31/38 (81.6)	-8.3 (-26.0, 10.5)

Source: Reviewer Table

Subgroups at EOT & SFU: Subgroup analyses at EOT & SFU were conducted for variables of interest. **Table 20** shows success rates for clinical status at EOT by stratification variables used at randomization (i.e. fever status, region, infection type). For the fever variable, treatment comparisons for dalbavancin appeared to more favorable (or less unfavorable) in patients with fever at baseline. For region, a large difference in success rates was observed across trials for the region of North America, where dalbavancin patients fared substantially worse vs. the comparator in Trial 301 but substantially better in Trial 302. For infection type, low success rates were observed in Trial 301 for patients with wound infections, especially in the dalbavancin arm.

Table 20: Clinical Status at EOT by Stratification Variables at Randomization (ITT)

Subgroup Variable Category	Trial 301 (n=573)			Trial 302 (n=739)		
	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)	Dalbavancin (N=371) n (%)	Comparator (N=368) n (%)	Difference (95% CI)
Fever Status						
Febrile	196/236 (83.1)	206/235 (87.7)	-4.6 (-11.1, 1.8)	271/303 (89.4)	258/303 (85.2)	4.3 (-1.0, 9.7)
Afebrile	38/52 (73.1)	41/50 (82.0)	-8.9 (-25.1, 7.6)	58/68 (85.3)	56/65 (86.2)	-0.9 (-13.2, 11.6)
Region						
North America	90/123 (73.2)	101/121 (83.5)	-10.3 (-20.6, 0.1)	105/115 (91.3)	95/114 (83.3)	8.0 (-0.7, 17.0)
Other Regions	144/165 (87.3)	146/164 (89.0)	-1.8 (-9.0, 5.4)	224/256 (87.5)	219/254 (86.2)	1.3 (-4.7, 7.3)
Infection Type						
Cellulitis	135/156 (86.5)	133/147 (90.5)	-3.9 (-11.3, 3.4)	174/198 (87.9)	167/202 (82.7)	5.2 (-1.8, 12.3)
Major Abscess	61/72 (84.7)	77/86 (89.5)	-4.8 (-16.2, 5.8)	81/91 (89.0)	78/87 (89.7)	-0.6 (-10.2, 9.0)
Wound Infection	38/60 (63.3)	37/52 (71.2)	-7.8 (-24.7, 9.8)	74/82 (90.2)	69/79 (87.3)	2.9 (-7.2, 13.4)

Source: Reviewer Table

Patients at EOT & SFU by Baseline Pathogen: In dalbavancin patients, clinical success rates at EOT & SFU in patients with *S.aureus*, MRSA and MSSA tended to be less favorable vs. the comparator in Trial 301, **Table 21.** These rates for dalbavancin were also substantially lower in Trial 301 vs. Trial 302. Comparisons for *S.pyogenes* were limited by small numbers.

Table 21: Success Rates at EOT & SFU by Baseline Pathogen (MicroITT)

Patient Success Rates by Pathogen	Trial 301		Trial 302	
	Dalbavancin (n=153)	Comparator (n=155)	Dalbavancin (n=184)	Comparator (n=174)
Clinical Success Rates at EOT				
S.aureus	94/122 (77.0%)	114/128 (89.1%)	124/135 (91.9%)	112/128 (87.5%)
MRSA	35/44 (79.5)	36/39 (92.3)	44/46 (95.7)	24/28 (85.7)
MSSA	59/78 (75.6)	77/88 (87.5)	80/89 (88.9)	88/101 (87.1)
S.agalactiae	1/3 (33.3)	5/6 (83.3)	8/9 (88.9)	7/8 (87.5)
S.anginosus[1]	4/7 (57.1)	12/13 (92.3)	13/15 (86.7)	10/12 (83.3)
S.pyogenes	12/12 (100)	12/14 (85.7)	23/25 (92.0)	21/22 (95.5)
Clinical Success Rates at SFU				
S.aureus	99/122 (81.1%)	118/128 (92.2%)	118/135 (87.4%)	111/128 (86.7%)
MRSA	37/44 (84.1)	34/39 (87.2)	38/46 (82.6)	23/28 (82.1)
MSSA	62/78 (79.5)	83/88 (94.3)	80/89 (89.9)	88/101 (87.1)
S.agalactiae	2/3 (66.7)	4/6 (66.7)	8/9 (88.9)	7/8 (87.5)
S.anginosus[1]	7/7 (100)	11/13 (84.6)	14/15 (93.3)	12/12 (100)
S.pyogenes	11/12 (91.7)	12/14 (85.7)	22/25 (88.0)	20/22 (90.9)

[1] Refers to the *S.anginosus* group which includes *S. anginosus*, *S.intermedius*, and *S. constellatus.*
Source: Reviewer Table

Patients at SFU by Creatinine Clearance: In **Table 22**, success rates for clinical status at SFU were compared for various levels of creatinine clearance (mL/min) at baseline. This analysis was performed to explore possible trends in which patients with more severe renal impairment could have less favorable outcomes while on dalbavancin vs. comparator therapy. However, there did not appear to be any relationship between creatinine clearance and clinical status of success at SFU. In fact, Trial 302 comparisons of dalbavancin in patients with more severe renal impairment (i.e. creatinine clearance of ’30 - < 60’ or ‘< 60’) appeared to be most favorable.

Table 22: Clinical Status at SFU by Creatinine Clearance (ITT)

	Trial 301 (n=573)			Trial 302 (n=739)		
mL/min	**Dalbavancin (N=288)** n (%)	**Comparator (N=285)** n (%)	**Difference (95% CI)**	**Dalbavancin (N=368)** n (%)	**Comparator (N=371)** n (%)	**Difference (95% CI)**
≥ 90	116/138 (84.1)	123/140 (88.3)	-3.8 (-12.2, 4.5)	149/172 (86.6)	154/177 (87.0)	-0.4 (-7.7, 6.9)
60 - < 90	69/79 (87.3)	79/89 (88.8)	-1.4 (-12.0, 8.7)	109/118 (92.4)	92/106 (86.8)	5.6 (-2.5, 14.3)
30 - < 60	50/56 (89.3)	44/47 (93.6)	-4.3 (-16.2, 7.9)	61/68 (89.7)	62/78 (79.5)	10.2 (-1.8, 22.1)
< 30	6/11 (54.5)	5/8 (62.5)	-8.0 (-47.8, 35.8)	7/9 (77.8)	3/7 (42.9)	34.9 (-14.0, 71.1)

Source: Reviewer Table

Concordance Analyses

Concordance at 48-72 hours & EOT: Concordance analyses of responders/non-responders at 48-72 hours and clinical success/failure at EOT are presented in **Table 23**. In Trial 301, considering only responders at 48-72 hours, 206/240 (85.8%) of patients in the dalbavancin arm were clinical successes at EOT versus 213/233 (91.4%) in the comparator arm. In Trial 302, 263/285 (92.3%) of patients in the dalbavancin arm were clinical successes at EOT versus 260/288 (90.3%) in the comparator arm.

Table 23: Concordance Analysis - Responder/Non-Responders at 48-72 Hours with Clinical Success/Failure at EOT (ITT)

Responder rates n (%)	**Dalbavancin N=288**	**Comparator N=285**	**Dalbavancin N=371**	**Comparator N=368**
	Responders (48-72 hrs)		**Non-responders (48-72 hrs)**	
Trial 301	n=240	n=233	n=48	n=52
Clinical success at EOT	206 (85.8)[1]	213 (91.4)[1]	28 (58.3)	34 (65.4)
Clinical failure at EOT	34 (14.2)	20 (8.6)	20 (41.7)	18 (34.6)
Trial 302	n=285	n=288	n=86	n=80
Clinical success at EOT	263 (92.3%)[2]	260 (90.3%)[2]	66 (76.7%)	54 (67.5%)
Clinical failure at EOT	22 (7.7%)	28 (9.7%)	20 (23.3%)	26 (32.5%)

[1] Treatment difference was -5.6% (95% CI: -11.5, 0.2)
[2] Treatment difference was 2.0% (95% CI: -2.7, 6.8)
Source: Reviewer Table

The reasons for failures in subjects who responded at 48-72 hours but failed at EOT are presented in **Table 24**. In Trial 301 there were a total of 34 & 20 early responders in the dalbavancin & comparator arms who became clinical failures at EOT. This included 8 dalbavancin and 6 comparator subjects that were declared to have an indeterminate outcome. These subjects lacked required data on lesion measurements and infection signs. Overall the receipt of non-study antibacterial drugs for ABSSSI and incomplete resolution of local signs of infection accounted for the greater number of failures at EOT among dalbavancin subjects.

Table 24: Reason for Failure at EOT among Responders at 48-72 hours

Responders at 48-72 hours	Trial 301		Trial 302	
	Dalbavancin n=240	Comparator n=233	Dalbavancin n=285	Comparator n=288
Failures at EOT (Clinical Failures & Indeterminates):	**34**	**20**	**22**	**28**
Indeterminates	**8**	**6**	**5**	**10**
No EOT visit, missing all measurement data	8	6	3	4
Missing temperature measurement only	**0**	**0**	**1**	**5**
Missing lesion measurement only	0	0	1	1
Clinical Failures	**26**	**14**	**17**	**18**
Lesion size at EOT is not decreased from Baseline	4	0	1	1
Temperature at EOT >37.6C	0	0	1	0
Local signs of infection have not resolved	22	13	11	11
Received non-study systemic antibacterial for ABSSSI	6	1	3	3
Death	0	1	0	0
Surgical intervention till EOT	1	0	7	5

Source: Reviewer Table

Concordance at 48-72 hours & SFU: The analyses of concordance of clinical response at 48-72 hours with complete resolution of local signs at SFU are presented in **Table 25**. In Trial 301, considering responders at 48-72 hours, 194/240 (80.8%) of patients in the dalbavancin arm later achieved complete resolution of local signs versus 207/233 (88.8%) in the comparator arm. In Trial 302, 235/285 (82.5%) of responders in the dalbavancin arm later achieved complete resolution of local signs versus 242/288 (84.0%) in the comparator arm. Considering only non-responders, success rates were lower for dalbavancin vs. comparator in Trial 301 but higher for

Trial 302. However, inferences in this subgroup were limited by the small numbers of patients who were non-responders. Note that overall success rates in non-responders across both trials were observed to be substantially lower than in responders, indicating a fairly strong relationship between clinical response at 48-72 hours and clinical success at SFU.

Table 25: Concordance Analysis- Responder/Non-Responders at 48-72 Hours with Complete/Incomplete Resolution of Local Signs at SFU (ITT)

Short-term Follow-up↓	**Dalbavancin N=288**	**Comparator N=285**	**Dalbavancin N=371**	**Comparator N=368**
	Responders (48-72 hrs)		**Non-Responders (48-72 hrs)**	
Trial 301	n=240	n=233	n=48	n=52
Complete resolution	194 (80.8%) [1]	207 (88.8) [1]	26 (54.2)	32 (61.5)
Incomplete resolution	46 (19.2)	26 (11.2)	22 (45.8)	20 (38.5)
Trial 302	n=285	n=288	n=86	n=80
Complete resolution	235 (82.5)[2]	242 (84.0)[2]	57 (66.3)	44 (55.0)
Incomplete resolution	50 (17.5)	46 (16.0)	29 (33.7)	36 (45.0)

[1] Treatment difference was -8.0% (95% CI: -14.5, -1.6).
[2] Treatment difference was -1.6% (95% CI: -7.8, 4.6).
Source: Reviewer Table

In **Table 26,** the Reviewer explored the reasons why responders were failing to achieve complete resolution of local signs at SFU. Lack of complete resolution of erythema was a major reason for dalbavancin patients. In Trial 301, there were 21 dalbavancin responders who failed to achieve complete resolution vs. 6 responders in the comparator arm. In Trial 302, there were 12 dalbavancin responders vs. 7 responders in the comparator arm. Another major reason for lack of complete resolution was missing data for local signs which had a strong influence on both treatments of both trials.

Table 26: Reasons for Incomplete Resolution at SFU among Responders at 48-72 hrs

	Trial 301		**Trial 302**	
	Dalbavancin N=240	Comparator N=233	Dalbavancin N=285	Comparator N=288
Incomplete resolution of local signs at SFU	**46**	**26**	**50**	**46**
Local signs unresolved:	25	12	26	24
− Erythema:	21	6	12	7

	Trial 301		Trial 302	
	Dalbavancin N=240	Comparator N=233	Dalbavancin N=285	Comparator N=288
− Heat/warmth:	5	1	0	1
− Tenderness:	5	6	4	11
− Swelling:	11	5	12	13
Missing local signs:	18	13	18	17
Use of non-study systemic antibacterials:	8	3	4	3
Surgical intervention:	2	0	7	6

Source: Reviewer Table

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Findings

Study Design & Conduct

Issues with the study design and conduct (including analyses) were as follows:

- **Lack of an appropriate non-inferiority margin and no pre-specified 'win/lose' criteria for later endpoints:** Currently, there is uncertainty in defining an appropriate non-inferiority margin beyond 72 hours and this prevents inferential testing for non-inferiority in later endpoints. Although the scientific interpretation may not be as clear, statistical testing could still be performed with pre-specified 'win/lose' criteria based on some 'allowable' lower confidence limit for the treatment difference. However, no such pre-specification was made in designing these trials. Due to these limitations, interpretation of findings at later endpoints may be subjective.

- **Definition of success criteria in clinical status endpoint:** The success criteria used in clinical status endpoint had several limitations. For example, the clinical status definition did not consider the local sign of erythema or the magnitude of the % reductions in lesion size at EOT and SFU. The clinical status definition also allowed successes to have incomplete resolution of several local signs at SFU (e.g. purulent drainage and discharge).

- **Highly influential factors in the clinical status endpoint:** Clinical status at EOT was unduly influenced by the clinical sign of heat/warmth. For example, Trial 301 showed that 30 subjects (19 dalbavancin vs. 11 comparator) were failures only due to the local sign of heath/warmth whereas the number of failures due only to each of the other reasons was much lower at a total of 3 or fewer subjects, as shown in **Table 14**. Clinical status at SFU

was also highly influenced by a single factor (i.e. the use of non-study systemic antibacterials).

- **Discordance of responder rates with clinical assessment at EOT:** Although early responder rates have a clear relationship with clinical success at later endpoints, there are still a large number of early responders who go on to fail at later endpoints. This can make interpretation of findings at early endpoints more problematic especially if there are substantial treatment differences in responders who fail at later assessments. Trial 301 showed a substantially higher failure rate in the dalbavancin arm among responders at EOT and SFU, **Table 23** & **Table 25**.

- **Potential influence of concomitant anti-inflammatory use:** Anti-inflammatory use can potentially confound the effect of the treatment on the primary outcome. In the combined treatment arms of Trials 301 & 302, there were 124 (22%) & 83 (11%) of patients with concomitant anti-inflammatory use in the first 72 hours following the start of study therapy. However, it is not clear whether the dalbavancin arm would have substantially benefitted from such confounding. For example, the inclusion of patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) between 48 and 72 hours (where confounding is most likely to occur) tended to result in less favorable treatment differences for dalbavancin patients, **Table 19**.

- **Missing/indeterminate data (especially at SFU):** There were a large number of missing/indeterminate outcomes at EOT and especially at SFU. As shown in **Table 12**, much of the treatment difference in success rates was due to imbalances in the number of indeterminates. Treatment differences in failure rates (excluding indeterminates) were substantially smaller than differences in success rates.

- **Data from 6 Patients in Trial 301 (Site 118):** OSI found that 6 patients from Trial 301 (Site 118) had no drug administration records and findings from these patients may be excluded at the Division's discretion.

  Note: The Reviewer noted some inconsistencies among other study sites as described in the next two bullets.

- **Investigator errors in measuring lesion size resulting in study biases:** Lesion measurements observed in Trial 302 suggested potential errors. For example, comparing proportions of patients with reductions in lesion area of exactly 0% at 48-72 hours, Trial 302 showed 15 patients with a exactly a 0% reduction vs. 0 (zero) patients in Trial 301. In addition, Trial 302 Site 903 (Estonia) showed 10 of 15 patients with a 0% reduction from baseline at 48-72 hours. Note that measurement error can make treatments appear to be more similar when in fact they are not and this can result in study biases under a non-inferiority design.

- **Unusually High Responder Rates at Study Sites:** In Trial 301, Site 607 (Ukraine) showed responder rates at 48-72 hrs of 36/36 (100%) for dalbavancin vs. 47/48 (97.9%) for the

comparator. Comparisons of overall response rates for Site 607 vs. All Other Sites were 98.8% vs. 79.8%, 19.1% (13.3, 23.2), p-value= $1.2x10^{-6}$ using Fisher's exact test.

Study Results

Issues with the study results were primarily related to Trial 301 for the following analyses which showed less favorable comparisons at later endpoints:

- **Clinical status at EOT/SFU**: In Trial 301, comparisons for these endpoints were substantially lower in the dalbavancin arm: 81.3% vs. 86.7%, -5.4% (-11.5%, 0.6%) at EOT and 83.7% vs. 88.1%, -4.4% (-10.2%, 1.3%) at SFU.

- **Reviewer sensitivity analyses (S1-S4)**: Compared to the above analyses of clinical status, Reviewer sensitivity analyses (S1-S4) for Trial 301 showed even less favorable comparisons when placing additional requirements on erythema/lesion size and other local signs. At EOT, differences (95% CIs) for S1 & S2 were less favorable at -6.4% (-12.8, -0.1) & -7.5% (-14.1%, -0.8%). At SFU, differences (95% CIs) for S3 & S4 were less favorable at -5.1% (-11.4, 1.3) & -7.5% (-14.0, -0.9), **Table 13**.

- **Concordance analyses:** Concordance analyses in Trial 301 showed that treatment comparisons were also unfavorable when considering only the subgroup of responders at 48-72 hours. When considering the concordance of early clinical response at 48-72 hours and clinical status at EOT (**Table 23**), success rates were 85.8% vs. 91.4%, -5.6% (-11.5, 0.2), and when considering the concordance of early clinical response at 48-72 hours and complete resolution of local signs at SFU (**Table 25**), success rates were 80.8% vs. 88.8%, -8.0% (-14.5, -1.6). These treatment differences were slightly larger in magnitude compared to treatment differences shown in **Table 13** in the ITT population (i.e. including both responders and non-responders) at -5.6% vs. -5.4% for clinical status at EOT and -8.0% vs. -7.5% for complete resolution of local signs at SFU.

- **Distributions in % reductions in lesion size:** When comparing treatments in Trial 301 based on the distribution of patients meeting various % reductions in lesion area at EOT and SFU, dalbavancin appeared to be less favorable across all categories of required % reductions. There also appeared to be a trend towards larger treatment differences as the required % reduction was increased, **Figure 4**.

- **Complete resolution of erythema in responders:** Treatment comparisons appeared to be especially unfavorable among responders in Trial 301, where 21/240 (8.8%) of dalbavancin responders vs. 6/233 (2.6%) of comparator responders failed to have complete resolution of erythema. In Trial 302, the corresponding comparisons were 12/285 (4.2%) vs. 7/288 (2.4%), **Table 26**.

- **Reviewer analyses excluding 6 Patients:** Reviewer analyses of key study endpoints excluding 6 patients due to lack of drug administration records appeared to be slightly less

favorable at later endpoints after excluding these 6 patients, **Table 35**. For example, the upper confidence limit of the 95% CI for the treatment difference in success rates at EOT crossed below 0 after the exclusion.

5.2 Collective Evidence

Trials 301 & 302 both demonstrated the non-inferiority of dalbavancin to comparator therapy based on early clinical response at 48-72 hours using a 10% margin. Therefore, overall evidence of efficacy and safety was considered to be adequate. However, there is still some uncertainty regarding efficacy at later endpoints, such as clinical status at EOT and SFU which were highly variable across trials, substantially favoring the comparator in Trial 301 and dalbavancin in Trial 302. There is also uncertainty related to the success criteria used in the clinical status endpoints of both trials since these criteria may fail to address improvements in local signs that would be expected at later assessments.

5.3 Conclusions and Recommendations

Trials 301 and 302 provided adequate evidence to support the use of dalbavancin in treating adults with ABSSSI based on non-inferiority comparisons of early clinical response rates at 48-72 hours as well as other supportive evidence. As dalbavancin was only studied in adults in Trials 301 and 302, we recommend that an adequate and well controlled study is conducted in pediatric patients under the age of 18 as a post marketing requirement/commitment.

5.4 Labeling Recommendations

Labeling negotiations are still ongoing. However, some of the major changes based on statistical recommendations made to the Applicant's initially proposed labels included the following:

- (b) (4)
-
- The recommendation to have a table of clinical success rates (by pathogen) evaluated at both 48-72 hours and SFU where clinical success rates were defined consistently with earlier efficacy analyses in the label (b) (4)
- (b) (4)

6. REFERENCES

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7. APPENDIX

Early endpoints (48-72 hrs)

Table 27 presents the various reasons clinical non-response at 48-72 hours. There did not appear to be any large imbalances within trials with respect to these reasons with the possible exception of patients with only an increase in lesion size in Trial 302 where there were more dalbavancin patients observed. It should be noted that missing data at 48-72 hours was minimal due to it being an early assessment with a wide window in which patients could still satisfy the endpoint on either of two visits (i.e. Day 3 and Day 4 visits).

Table 27: Reasons for Clinical Non-Response at 48-72 hours

Clinical Non-Responders: Reasons:	**Trial 301**		**Trial 302**	
	Dalbavancin N=48	**Comparator N=52**	**Dalbavancin N=86**	**Comparator N=80**
Only Increase in Lesion Size	13 (27.1)	13 (25.0)	25 (29.1)	18 (22.5)
Only Febrile	14 (29.2)	15 (28.8)	27 (31.4)	28 (35.0)
No Evidence of Fever, but Temperature Criteria not Met[1]	12 (25.0)	13 (25.0)	21 (24.4)	18 (22.5)
Both Increase in Lesion Size and Febrile	3 (6.3)	3 (5.8)	5 (5.8)	4 (5.0)
Both Increase in Lesion Size and Temperature Criteria not Met	3 (6.3)	1 (1.9)	0	1 (1.3)
Died within the First 72 hrs	0	1 (1.9)	0	0
Initiated New Systemic Antibacterial within First 72 hrs[2]	2 (4.2)	2 (3.8)	4 (4.7)	5 (6.3)
Missing Data at Baseline for Lesion Measurement	4 (8.3)	1 (1.9)	3 (3.5)	0
Missing Data at 48-72 hrs for Lesion Measurement Only	1 (2.1)	3 (5.8)	1 (1.2)	1 (1.3)
Missing Data at 48-72 hrs for Determination of Fever Only[3]	0	1 (1.9)	0	1 (1.3)
Missing Data at 48-72 hrs for Both Lesion Measurement and Determination of Fever	6 (12.5)	5 (9.6)	7 (8.1)	9 (11.3)

[1] The patient had at least one temperature measurement, but did not have three temperature measurements 3 - 9 hrs apart in the 48-72 hour window and no temperature > 37.6C after the 48 hour time point.
[2] The patient initiated a new systemic antibacterial with Gram-positive activity for the abSSSI under study within the first 72 hours.
[3] All temperature data in the 48-72 hour window are missing for the patient.
Source: Partially Adapted from Applicant Table 14.6.1.2

Table 28 shows analyses of responders (defined as patients achieving ≥ 20% reduction in lesion area at 48-72 hours) by stratification factors used at randomization. For patients with fever at baseline, treatment differences in responder rates favored the comparator in Trial 301 and dalbavancin in Trial 302. For the variable of region, clinical response rates were also inconsistent across trials, being lower in North America versus all other regions in Trial 301 but substantially higher in Trial 302. Considering the infection types, dalbavancin was shown to be slightly less favorable across trials in patients with cellulitis vs. other infection types.

Table 28: Responder Rates for ≥ 20% Reduction in Lesion Area Only at 48-72 hours by Stratification Variables at Randomization (ITT)

Stratifying Variable	Trial 301 (n=573)			Trial 302 (n=739)		
	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)	Dalbavancin (N=371) n (%)	Comparator (N=368) n (%)	Difference (95% CI)
Fever at Baseline						
Fever	215/236 (91.1)	222/235 (94.5)	-3.4 (-8.3, 1.4)	269/303 (88.8)	260/303 (85.8)	3.0 (-2.4, 8.4)
No fever	44/52 (84.6)	37/50 (74.0)	10.6 (-5.3, 26.6)	56/68 (82.4)	56/65 (86.2)	-3.8 (-16.6, 9.0)
Region						
North America	108/123 (87.8)	104/122 (86.0)	1.9 (-6.8, 10.6)	107/115 (93.0)	106/114 (93.0)	0.1 (-7.1, 7.2)
All other regions	151/165 (91.5)	155/164 (94.5)	-3.0 (-8.9, 2.7)	218/256 (85.2)	210/254 (82.7)	2.5 (-3.9, 8.9)
Infection Type						
Cellulitis	136/156 (87.2)	133/147 (90.5)	-3.3 (-10.6, 4.0)	163/198 (82.3)	168/202 (83.2)	-0.9 (-8.3, 6.6)
Major abscess	67/72 (93.1)	78/86 (90.7)	2.4 (-7.1, 11.5)	85/90 (94.4)	80/87 (92.0)	2.5 (-5.5, 10.9)
Wound infection	56/60 (93.3)	48/52 (92.3)	1.0 (-9.5, 12.5)	77/82 (83.9)	80/79 (86.1)	7.8 (-1.6, 18.0)

Source: Reviewer Table

Later endpoints (EOT & SFU)

Table 29 shows success rates at EOT and SFU in patients who were evaluable at those visits. In Trial 301, lower success rates were observed in the dalbavancin arm with a treatment difference of -4.4% (-10.0, 1.2). Slightly lower rates were also observed at SFU with a difference of -2.3% (-6.6, 2.0). In Trial 302, success rates were similar between treatments.

Table 29: Reviewer Analyses of Clinical Status, Success Rates at EOT & SFU in Clinically Evaluable Patients

Clinical Status	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)[1]
Trial 301	N=288	N=285	
Success, CE-EOT	214/246 (87.0%)	222/243 (91.4%)	-4.4% (-10.0, 1.2)
Success, CE-SFU	212/226 (93.8%)	220/229 (96.1%)	-2.3% (-6.6, 2.0)
Trial 302	N=371	N=368	
Success, CE-EOT	303/324 (93.5%)	280/302 (92.7%)	0.8% (-3.3, 5.0)
Success, CE-SFU	283/294 (96.3%)	257/272 (94.5%)	1.8% (-1.8, 5.6)

[1] 95% CIs were calculated using the Miettinen and Nurminen approach, adjusted for baseline fever status.
[2] Clinical status at EOT was a pre-specified secondary endpoint.
Source: Reviewer Table

In **Table 30**, treatment differences in the investigator assessment at EOT and SFU favored the comparator in Trial 301 and dalbavancin in Trial 302. In both trials, treatment differences for investigator assessment at EOT and SFU were smaller than treatment differences for clinical status at EOT and SFU.

Table 30: Clinical Success Rates from Investigator Assessment at EOT, SFU (ITT)

	Trial 301			Trial 302		
Endpoint	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)	Dalbavancin (N=371) n (%)	Comparator (n=368) n (%)	Difference (95% CI)
Investigator Assessment at EOT	260 (90.3)	262 (91.9)	-1.7 (-6.5, 3.1)	342 (92.2)	332 (90.2)	2.0 (-2.2, 6.2)
Investigator Assessment at SFU	248 (86.1)	255 (89.5)	-3.4 (-8.8, 2.0)	326 (87.9)	317 (86.1)	1.7 (-3.2, 6.6)

Source: Reviewer Table

In **Table 31**, responder rates by pathogen (responders defined as those with a ≥ 20% reduction in lesion area at 48-72 hours) were generally similar across trials in both treatment arms, tending to be slightly higher in the dalbavancin arm for patients with *S.aureus* at baseline. When considering responder rates based on a 20% reduction in lesion area rather than on cessation of spread of lesion and absence of fever (primary endpoint) as in **Table 18**, Trial 301 comparisons of responder rates favored dalbavancin for *S.aureus* and the comparator for *S.pyogenes.*

Table 31: Responder Rates Based on a ≥ 20% Reduction in Lesion Area at 48-72 Hours by Baseline Pathogen (MicroITT)

Baseline Pathogen	Trial 301		Trial 302	
	Dalbavancin (N=153)	Comparator (N=155)	Dalbavancin (N=184)	Comparator (N=174)
S.aureus	115/122 (94.3)	117/128 (91.4)	124/135 (91.9)	115/128 (89.8)
MRSA	41/44 (93.2)	33/39 (84.6)	42/46 (91.3)	26/28 (92.9)
MSSA	74/78 (94.9)	83/88 (94.3)	82/89 (92.1)	90/101 (89.1)
S. agalactiae	2/3 (66.7)	4/6 (66.7)	8/9 (88.9)	6/8 (75.0)
S. anginosa[1]	7/7 (100)	13/13 (100)	14/15 (93.3)	12/12 (100)
S.pyogenes	10/12 (83.3)	12/14 (85.7)	22/25 (88.0)	15/22 (68.2)

[1] The *S.anginosus* group includes *S. anginosus*, *S.intermedius*, and *S. constellatus.*
Source: Reviewer Table

Table 32 & **Table 33** show complete resolution rates for individual local signs at EOT and SFU. There were no notable treatment differences in each of the local signs with the exception of erythema in which differences strongly favored the comparator in Trial 301 but tended to be similar in Trial 302.

Table 32: Complete Resolution of Individual Local Signs at EOT (ITT)

Local Sign	Trial 301 (n=573)			Trial 302 (n=739)		
	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)	Dalbavancin (N=371) n (%)	Comparator (N=368) n (%)	Difference (95% CI)
Purulent drainage	259 (89.9)	264 (92.6)	-2.7 (-7.5, 2.0)	351 (94.6)	346 (94.0)	0.6 (-2.9, 4.1)
Erythema	198 (68.8)	221 (77.5)	-8.8 (-16.0,-1.5)	296 (79.8)	290 (78.8)	1.0 (-4.9, 6.9)
Fluctuance	270 (93.8)	268 (94.0)	-0.3 (-4.4, 3.8)	358 (96.5)	353 (95.9)	0.6 (-2.3, 3.5)
Heat/ warmth	244 (84.7)	252 (88.4)	-3.7 (-9.4, 1.9)	344 (92.7)	336 (91.3)	1.4 (-2.6, 5.4)
Swelling/ induration	230 (79.9)	236 (82.8)	-3.0 (-9.4, 3.5)	294 (79.3)	289 (78.5)	0.7 (-5.2, 6.6)
Tenderness to palpation	212 (73.6)	220 (77.2)	-3.6 (-10.6, 3.5)	281 (75.7)	282 (76.6)	-0.9 (-7.0, 5.3)

Source: Reviewer Table

Table 33: Complete Resolution Rates of Individual Local Signs at SFU (ITT)

Local Sign	Trial 301 (n=573)			Trial 302 (n=739)		
	Dalbavancin (N=288) n (%)	Comparator (N=285) n (%)	Difference (95% CI)	Dalbavancin (N=371) n (%)	Comparator (N=368) n (%)	Difference (95% CI)
Purulent drainage	258 (89.6)	258 (90.5)	-0.9 (-6.0, 4.1)	342 (92.2)	334 (90.8)	1.4 (-2.7, 5.6)
Erythema	233 (80.9)	248 (87.0)	-6.1 (-12.2, -0.1)	325 (87.6)	325 (88.3)	-0.7 (-5.5, 4.0)
Fluctuance	258 (89.6)	260 (91.2)	-1.6 (-6.6, 3.3)	344 (92.7)	334 (90.8)	2.0 (-2.1, 6.1)
Heat/warmth	255 (88.5)	259 (90.9)	-2.3 (-7.4, 2.7)	343 (92.5)	333 (90.5)	2.0 (-2.1, 6.1)
Swelling	253 (87.9)	254 (89.1)	-1.3 (-6.6, 4.0)	330(89.0)	315 (85.6)	3.4 (-1.5, 8.2)
Tenderness	243 (84.4)	250 (87.7)	-3.3 (-9.1, 2.4)	324(87.3)	311 (84.5)	2.8 (-2.2, 7.9)

Source: Reviewer Table

In Study 301, treatment comparisons remained similar following the exclusion of 6 patients at 83.0% vs. 82.0%, 1.0% (-5.1%, 7.4%) for the primary endpoint and 89.8% vs. 90.8%, -1.1% (-5.9%, 4.0%) when defining responders based on a 20% reduction in lesion area, **Table 34**.

Table 34: Reviewer Analyses: Responder Rates at 48-72 hours Excluding 6 Patients

Responder Rates:	Trial 301			Trial 302		
	Dalbavancin (N=283) n (%)	Comparator (N=284) n (%)	Difference (95% CI)[1]	Comparator (N=371) n (%)	Dalbavancin (N=368) n (%)	Difference (95% CI)[1]
Primary Cessation of spread & afebrile at 48-72 hrs	235 (83.0)	233 (82.0)	1.0 (-5.1, 7.4)	285 (76.8)	288 (78.3)	-1.5 (-7.4, 4.6)
Key Secondary ≥ 20% reduction in lesion area at 48-72 hrs	254 (89.8)	258 (90.8)	-1.1 (-5.9, 4.0)	325 (87.6)	316 (85.9)	1.7 (-3.2, 6.7)

[1] 95% CIs were calculated using the Miettinen and Nurminen approach, adjusted for baseline fever status.
Responders could not use new non-study systemic antibiotics or have a death in the study period up to 48-72 hrs.
Six patients were excluded due to lack of drug administration records: 5 in the dalbavancin arm (118-053 118-068 118-079 118-108 118-109) and one in the comparator arm (118-083).
Source: Reviewer Table

In **Table 35**, Trial 301 comparisons at later endpoints became slightly less favorable following the exclusions at 80.9% (dalbavancin) vs. 87.0% (comparator), a difference of -6.1% (95% CI: -12.2, -0.0) at EOT and 83.4% vs. 88.4%, -5.0% (-10.8, 0.8) at SFU. Prior to these exclusions, treatment differences were -5.4% (-11.5, 0.6) at EOT and -4.4% (-10.2%, 1.3%), **Table 12**.

Table 35: Reviewer Analyses of Clinical Status, Success Rates at EOT & SFU (ITT), Excluding 6 Patients

Clinical Status at EOT[2] and SFU Outcome	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)[1]
Trial 301	N=283	N=284	
Success, EOT	**229 (80.9%)**	**247 (87.0%)**	**-6.1% (-12.2, -0.0)**
Failure	40 (14.1)	29 (10.2)	3.9
Indeterminate	14 (4.9)	8 (2.8)	2.1
Success, SFU	**236 (83.4%)**	**251 (88.4%)**	**-5.0% (-10.8, 0.8)**
Failure	18 (6.4)	13 (4.6)	1.8
Indeterminate	29 (10.2)	20 (7.0)	3.2
Trial 302	N=371	N=368	
Success, EOT	**329 (88.7%)**	**314 (85.3%)**	**3.4% (-1.5, 8.3)**
Failure	32 (8.6)	34 (9.2)	-0.6
Indeterminate	10 (2.7)	20 (5.4)	-2.7
Trial 302	N=371	N=368	
Success, SFU	**327 (88.1%)**	**311 (84.5%)**	**3.6% (-1.3, 8.7)**
Failure	18 (4.9)	23 (6.3)	-1.4
Indeterminate	26 (7.0)	34 (9.2)	-2.2

[1] 95% CIs were calculated using the Miettinen and Nurminen approach, unadjusted.
[2] Clinical status at EOT was a pre-specified secondary endpoint.
Six patients were excluded due to lack of drug administration records: 5 in the dalbavancin arm (118-053 118-068 118-079 118-108 118-109) and one in the comparator arm (118-083).
Source: Reviewer Table

Other Analyses

Table 36 provides some of the reasons for use of non-study antibiotics at SFU and the days in which they were initiated. The most common reasons for non-study systemic antibacterial use related to either an 'insufficient therapeutic effect' or 'primary ABSSSI site, after study therapy'. There were no consistent trends across trials favoring either treatment with respect to reasons for non-study systemic antibacterial use.

Table 36: Reasons for Use of Non-Study Antibiotics at SFU, Trials 301 & 302 (ITT)

Reasons for use of non-study systemic antibacterials (more than one may apply):	Trial 301		Trial 302	
	Dalbavancin (N=16)	**Comparator (N=7)**	**Dalbavancin (N=11)**	**Comparator (N=15)**
Insufficient therapeutic effect: Start of Antibacterial Use:	**n=8** Days: 3, 4, 6, 8, 14, 15, 16, 17	**n=5** Days: 3, 3, 7, 15, 24	**n=3** Days: 2, 4, 12	**n=5** Days: 3, 4, 6, 11, 15
Adjunctive therapy, gram negative pathogen: Start of Antibacterial Use:	**n=3** Days: 1,1,1	**n=1** Day: 2	**n=3** Days: 1,1, 9	**n=4** Days: 1, 1, 3, 10
Primary ABSSSI site, after study therapy: Start of Antibacterial Use:	**n=8** Days: 5, 6, 6, 14, 14, 15, 17, 28	**n=3** Days: 2, 15, 25	**n=8** Days: 2, 3, 8, 10, 13, 13,18, 23	**n=12** Days: 2, 3, 3, 9, 14, 15, 15, 15, 15, 15, 18, 21
Other: Start of Antibacterial Use:	**n=4** Days: 1, 2, 2, 27	**n=0**	**n=3** Days: 2, 4, 28	**n=3** Days: 2, 14, 25

Source: Reviewer Table

Statistical Details

Estimation of Confidence Limits Using the Miettinin and Nurminen Approach:

The two-sided 95% CI for non-inferiority testing based on the difference of clinical response rates at 48-72 hours will be computed using the method proposed for stratified designs by Miettinen and Nurminen. For notation purposes, assume 1 represents the dalbavancin group (Group 1), 2 represents the vancomycin/linezolid group (Group 2), and i represents the ith stratum. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation for the CI as follows: $W_i = (n_{1i} * n_{2i})/ (n_{1i} + n_{2i})$.

Based on Miettinen and Nurminen, the two-sided 95% CI is given by the roots for $RD = p_1 - p_2$ of the following equation:

$$\chi_\alpha^2 = \frac{(\hat{p}_1 - \hat{p}_2 - RD)^2}{\sum_i \left(\frac{W_i}{\sum_i W_i}\right)^2 \tilde{V}_i}$$

where x^2 is the cut point of size α from the chi-square distribution (x^2_α =3.84 for two-sided 95% CI); RD is the difference between the two population rates ($RD = p_1 - p_2$); $\hat{p}_1$ = the observed weighted average (across the i strata) proportion in Group 1; weighted average (across the i strata) proportion in Group 2; and $\hat{p}_2$ = the observed weighted average (across the i strata) proportion in Group 2; and

$$\tilde{V}_i = \left[\frac{\tilde{p}_{1i}(1-\tilde{p}_{1i})}{n_{1i}} + \frac{\tilde{p}_{2i}(1-\tilde{p}_{2i})}{n_{2i}}\right]\frac{n_{1i}+n_{2i}}{n_{1i}+n_{2i}-1}$$

where n_{1i} = number of patients in Group 1 in the ith stratum; n_{2i} = number of patients in Group 2 in the ith stratum; $\tilde{p}_1 = \tilde{p}_2 + RD$; and $\tilde{p}_2$ is the maximum likelihood estimate for p_2 as a function of RD and under the constraint $p_1 = p_2 + RD$.

As stated above, the two-sided 95% CI for the difference in rates is given by the roots for $RD = p_1 - p_2$ from the equation above. But this equation does not allow for explicit solution for RD. Therefore, a numerical algorithm will be used to obtain the two roots (CI) for RD. This CI approach corresponds to the non-inferiority test (a p-value approach) proposed by Farrington and Manning[6].

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/s/

CHRISTOPHER E KADOORIE
05/12/2014

THAMBAN I VALAPPIL
05/12/2014

DIONNE L PRICE
05/13/2014
Concur with overall conclusion

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 21883 **Applicant: Durata Therapeutics, Inc.** **Stamp Date: 9/26/13**

Drug Name: Dalbavancin **NDA/BLA Type: 505(b)(1)**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	**X**			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**X**			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	**X**			
Appropriate references for novel statistical methodology (if present) are included.	**X**			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Safety data organized to permit analyses across clinical trials in the NDA/BLA.	**X**			**However, datasets do not strictly follow CDISC format. For example, values for the subject ID variable are not consistent across individual and integrated datasets (e.g. DUR001301-0101-0028 vs. DUR001301-101-028). Also, the date variables in the DUR001-301 & DUR001-302 ADAM datasets are defined as character instead of numeric.**
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	**X**			**Several approaches are defined for imputing missing data.**

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/s/

CHRISTOPHER E KADOORIE
11/21/2013

THAMBAN I VALAPPIL
11/25/2013

Non-Inferiority Margin Justification for Complicated Skin and Skin Structure Infections using Vancomycin as the Active Comparator

(b) (4)

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Scott Komo
12/14/2007 11:24:42 PM
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Thamban Valappil
12/18/2007 04:46:30 PM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-883 / N000

Drug Name: Dalbavancin powder for injection (b) (4) 500 mg)

Indication(s):

Applicant: Vicuron Pharmaceutical Inc. a subsidiary of Pfizer Inc.

Date(s): 6/19/07 (letter); 6/19/07 (stamp).

Review Priority: Standard

Biometrics Division: DBIV

Statistical Reviewer: Scott Komo, DrPH

Concurring Reviewers: Thamban Valappil, Ph.D.

Medical Division: Division of Anti-Infective and Ophthalmology Products

Clinical Team: Janice Pohlman, MD, MPH
Sumathi Nambiar, MD, MPH

Project Manager: Christopher Davi, MS

Keywords: active control/non-inferiority, delta choice (active control)

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1. EXECUTIVE SUMMARY

This submission contains the Sponsor's complete response to approvable letters that were issued on 6/21/06 (submission date: 12/20/05). The Sponsor submitted an original new drug application (NDA) for Dalbavancin on 12/21/04. Subsequently, an approvable letter was issued on 9/21/05 to the Applicant listing the deficiencies requiring response prior to approval. The two deficiencies were chemistry and manufacturing issues related to the isolated intermediate storage and reaching an agreement between FDA and Applicant on final labeling.

On 12/20/05, the Sponsor submitted a complete response to the approvable letter received on 6/21/05. Subsequently, an approvable letter was issued on 6/21/06 to the Applicant listing the deficiencies requiring response prior to approval. The deficiencies were chemistry and manufacturing issues related to high bacterial endotoxin levels in an active pharmaceutical ingredient and drug lot and to provide a mediation plan to address the bacterial endotoxins.

On 6/20/07, the Sponsor submitted a complete response to the June 21, 2006 approvable letter. Subsequently on 7/7/07, the Agency sent an information request to the Sponsor requesting justification for the (b) (4) non-inferiority (NI) margin used in study VER001-9 as well as requesting that the Sponsor submit a proposal for a thorough QT study.

1.1 Conclusions and Recommendations

(b) (4)

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/s/

Scott Komo
12/12/2007 11:20:42 AM
BIOMETRICS

Thamban Valappil
12/12/2007 11:37:19 AM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-883 / N000
Drug Name:	(b) (4) (dalbavancin)
	Powder for Injection (intravenous infusion) (b) (4) 500 mg
Indication(s):	Complicated Skin and Skin Structure Infections (cSSSI)
Applicant:	Vicuron Pharmaceuticals Inc.
Date(s):	Stamp Date: 21 December 2004
	PDUFA Goal Date: June 21, 2005
	Extended to September 21, 2005
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	B. Sue Bell, Ph.D.
Concurring Reviewers:	Daphne Lin, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmology Products
Clinical Team:	Sumathi Nambiar, M.D. Clinical Team Leader
	Janice Pohlman, M.D. Clinical Reviewer for Efficacy
	Menfo Imoisili, M.D. Clinical Reviewer for Safety
Project Manager:	J. Christopher Davi

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LIST OF TABLES

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In a single study of complicated skin and skin structure (VER001-9), dalbavancin demonstrated noninferiority to linezolid in the co-primary efficacy analyses of clinical response at test-of-cure in the Intent-to-Treat (ITT) and in the Clinically Evaluable (CE) populations. In a supportive study of uncomplicated skin and skin structure infections requiring parenteral therapy (VER001-8), dalbavancin demonstrated noninferiority to cefazolin.

1.2 Brief Overview of Clinical Studies

There were a total of three (3) phase-3 studies submitted. Study VER001-9 in complicated skin and skin structure infections (cSSSI) is the confirmatory study and Study VER001-8 in uncomplicated skin and skin structure infections is supportive. Both studies were randomized, double-blind, multi-center, and multi-national studies. In addition, study VER001-16 in either complicated or uncomplicated SSSI with suspected or confirmed MRSA requiring parenteral therapy was a randomized open-label Phase 3 study conducted in Canada and the US. Because VER001-16 was open label it was not reviewed for efficacy but was used to augment the safety database.

1.2.1 Study VER001-9 Complicated Skin and Skin Structure Infections (cSSSI)

Study VER001-9 was a phase-3 multi-center, randomized, double-blind (third party unblinded) double-dummy comparison of the safety and efficacy of IV dalbavancin versus IV linezolid/oral linezolid in patients with complicated SSSI with suspected or confirmed Gram-positive bacterial pathogens requiring parenteral therapies. Patients were randomly assigned (2:1 ratio) to receive either IV dalbavancin or IV linezolid/oral linezolid intravenously for up to 14 days.

A total of 3417 patients were screened with 873 patients randomized. Nineteen (19) patients did not receive study drug and 854 patients received at least 1 dose of the assigned study drug and constituted the ITT population: 571 patients received dalbavancin and 283 patients received linezolid. The study was conducted at 65 centers in 7 countries with 84% being treated in the US with the remaining being treated in Latvia, Lithuania, Canada, United Kingdom, Estonia, and Germany.

1.2.2 Study VER001-8 Uncomplicated Skin and Skin Structure Infections (uSSSI)

Study VER001-8 was a phase-3 multi-center, randomized, double-blind (third party unblinded) double-dummy comparison of the safety and efficacy of IV dalbavancin versus IV cefazolin/oral cefazolin in patients with uncomplicated SSSI with suspected or confirmed Gram-positive bacterial pathogens requiring parenteral therapies Patients were randomly assigned (2:1 ratio) to receive either IV dalbavancin or IV cefazolin/oral cefazolin for up to 14 days.

A total of 565 patients were enrolled in this study with 12 patients not receiving study drug. A total of 553 patients received at least 1 dose of the assigned study drug and constituted the ITT population: 367 patients received dalbavancin and 186 patients received cefazolin. The study was conducted at 70 centers in 7 countries with 54% being treated in the US with the remaining being treated in Latvia, Canada, Estonia, Germany, United Kingdom, and Italy.

1.3 Statistical Issues and Findings

1.4 Safety Issues

In the Phase 3 studies VER001-9, VER001-8, and VER001-16 in skin and skin structure infections, 6 patients treated with dalbavancin died while 3 patients treated with a comparator died. The frequency of death is consistent with the 2:1 randomizations and the deaths were not considered to be drug related. In addition in Phase 2 study VER001-4 of patients with catheter-related blood stream infections, 3 patients treated with dalbavancin died while 2 patients treated with vancomycin died. None were considered related to study medication.

The medical officer, Dr. Imoisili's review provides detailed safety information.

2 INTRODUCTION

2.1 Overview

Dalbavancin is a semi-synthetic glycopeptide antibiotic that is being developed as an intravenous treatment for severe Gram-positive bacterial infections, including infections caused by MRSA. In a Phase 2 study VER001-5, dalbavancin administered as an initial dose of 1000 mg followed 1 week later by a second dose of 500 mg appeared well-tolerated and more effective for treatment of Gram-positive bacterial SSSI than either the single dose dalbavancin regimen or standard antibiotic therapies. The once weekly IV dosing is in contrast to comparators that use q12h or q8h dosing for IV with possible switch or oral dosing.

This new drug application contains three Phase 3 studies. Sponsor reports results for one confirmatory study VER001-9 conducted in complicated skin and skin structure infections(cSSSI) and one supportive study VER001-8 conducted in uncomplicated skin and skin structure infections (uSSSI) that required IV therapy. The comparator in VER001-9 was IV linezolid 600 mg q12h with possible switch to oral linezolid 600 mg q12h. The comparator in VER001-8 was 500 mg q8h with possible switch to oral cefazolin 500 mg q6h. In addition, Sponsor includes an open-label Phase 3 study VER001-16 in skin and skin structure infections that required IV therapy.

In addition to Phase 2 pilot study VER001-5, Sponsor conducted VER001-4 as a Phase 2, randomized, open-label, multi-center study to evaluate the safety and efficacy of dalbavancin versus vancomycin in the treatment of catheter-related bloodstream infections with suspected or confirmed Gram-positive bacterial pathogens. Seventy-five patients were randomized and 64 patients completed the study. Sponsor reported that patients in the microbiological ITT population at TOC who received dalbavancin (87.0%, 95% CI: 73.2, 100.0) had a higher success rate than patients who received vancomycin (50.0%, 95% CI: 31.5, 68.5).

2.2 Data Sources

The datasets analyzed are in the CDER Electronic Document Room (EDR) in the following folders:

\\Cdsesub1\n21883\N_000\2005-02-24\CD_B\crt\datasets\VER001-9\
\\Cdsesub1\n21883\N_000\2005-02-24\CD_A\crt\datasets\VER001-8\
\\Cdsesub1\n21883\N_000\2005-02-24\CD_A\crt\datasets\VER001-16\
\\Cdsesub1\n21883\N_000\2005-02-24\CD_A\crt\datasets\ISS\

Statistical Reviewer's Comment: *On the request of the FDA, the Sponsor submitted revised datasets. Datasets originally submitted by the sponsor are located in the EDR in the folder \\cdsesub1\N21883\N_000\2004-12-21\crt\datasets. The statistical reviewer's 45-day fileability review documents the changes requested and made by the Sponsor. During the course of the review, the ISS data was converted to CDISC Study Data Tabulation Model format to support use of visualization and data mining tools. Additional inconsistencies in the data were addressed during the conversion such as use of multiple versions of MedDRA for coding adverse events and laboratory values that used different units in the U.S. than were used at the Canadian and European sites.*

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The medical officer, Dr. Pohlman's review provides detailed clinical information and discussion.

3.1.1 Study VER001-9 Complicated Skin and Skin Structure Infections (cSSSI)

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Revised to removed footer and add Bell to cc list

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