CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021883Orig1s003

Trade Name:	Dalvance
Generic Name:	Dalbavancin Hydrochloride Powder for Injection, 500 mg
Sponsor:	AbbVie Inc.
Approval Date:	January 20, 2016
Indication:	For acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms.

CENTER FOR DRUG EVALUATION AND RESEARCH

021883Orig1s003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-883/S-003

SUPPLEMENT APPROVAL

Durata Therapeutics International, B.V.
c/o Durata Therapeutics, Inc.
Attention: Nicole L. Bradley, PharmD
Director, Regulatory Affairs
Harborside Financial Center, Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Bradley:

Please refer to your Supplemental New Drug Application (sNDA) dated July 20, 2015, received July 20, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DALVANCE (dalbavancin hydrochloride) 500 mg, Powder for Injection.

This "Prior Approval" supplemental new drug application provides for the addition of a 1500 mg single-dose regimen for DALVANCE for the treatment of adult patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at:

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-883/S-003**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We remind you of your previous PREA postmarketing requirements (PMRs) specified in our May 23, 2014, original NDA approval letter. We note that the following two studies will evaluate the use of both a single-dose and two-dose regimen in children:

- **2145-3:** Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from 3 months to 17 years of age with ABSSSI.

As noted in the deferral extension granted letter dated December 16, 2015, you will conduct this study according to the following schedule:

Study Completion:	June 2017
Final Report Submission:	December 2017

- **2145-4:** Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in neonates/infants from birth to less than 3 months of age with ABSSSI.

The timetable you submitted on May 22, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2016
Study Completion:	December 2019
Final Report Submission:	June 2020

Submit the protocols to your IND 60,613 with a cross-reference letter to NDA 21-883.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies.

When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We also remind you that there are other postmarketing requirements and postmarketing commitments listed in our May 23, 2014, approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf.

Information and Instructions for completing the form can be found at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see:

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES: Content of Labeling
Carton and Container Labeling

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

/s/

SUMATHI NAMBIAR
01/20/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DALVANCE® safely and effectively. See full prescribing information for DALVANCE.

DALVANCE (dalbavancin) for injection, for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------
- Dosage and Administration (2) 01/2016

----------INDICATIONS AND USAGE----------
DALVANCE is indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms. (1.1)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DALVANCE and other antibacterial drugs, DALVANCE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Dosage in patients with normal or impaired renal function (2.1, 2.2):

Estimated CrCl	Single Dose Regimen	Two-Dose Regimen
≥ 30 mL/min or on regular hemodialysis	1500 mg	1000 mg followed one week later by 500 mg
< 30 mL/min and not on regular hemodialysis	1125 mg	750 mg followed one week later by 375 mg

- Administer by intravenous infusion over 30 minutes (2.1, 2.3)
- See Full Prescribing Information for instructions on reconstitution of lyophilized powder and preparation of injection (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 500 mg of lyophilized powder in a vial for reconstitution (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to dalbavancin (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious hypersensitivity (anaphylactic) and skin reactions have been reported with glycopeptide antibacterial agents, including DALVANCE; exercise caution in patients with known hypersensitivity to glycopeptides. (5.1)
- Rapid intravenous infusion of glycopeptide antibacterial agents can cause reactions. (5.2)
- ALT elevations with DALVANCE treatment were reported in clinical trials. (5.3)
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including DALVANCE. Evaluate if diarrhea occurs. (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions in patients treated with DALVANCE were nausea (4.7%), headache (3.8%), and diarrhea (3.4%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Durata Therapeutics, Inc. at 1-855-387-2825 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------USE IN SPECIFIC POPULATIONS----------
Dosage adjustment is required in patients whose creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised 01/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATION AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

DALVANCE® (dalbavancin) for injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI), caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*) *and Enterococcus faecalis (vancomycin susceptible strains).*

1.2 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DALVANCE and other antibacterial agents, DALVANCE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage Regimen

The recommended dosage regimen of DALVANCE in patients with normal renal function is 1500 mg, administered either as a single dose, or 1000 mg followed one week later by 500 mg. DALVANCE should be administered over 30 minutes by intravenous infusion *[see Dosage and Administration (2.3)]*.

2.2 Dosage in Patients with Renal Impairment

In patients with renal impairment whose known creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis, the recommended regimen of DALVANCE is 1125 mg, administered as a single dose, or 750 mg followed one week later by 375 mg (see Table 1). No dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis, and DALVANCE can be administered without regard to the timing of hemodialysis *[see Use in Specific Populations (8.5), Clinical Pharmacology (12.3)]*.

Table 1. Dosage of DALVANCE in Patients with Renal Impairment

Estimated CrCl*	DALVANCE Single Dose Regimen**	DALVANCE Two-Dose Regimen**
≥ 30 mL/min or on regular hemodialysis	1500 mg	1000 mg followed one week later by 500 mg
< 30 mL/min and not on regular hemodialysis	1125 mg	750 mg followed one week later by 375 mg

* as calculated using the Cockcroft-Gault formula

** administered intravenously over 30 minutes

2.3 Preparation and Administration

DALVANCE (dalbavancin) for injection must be reconstituted with either Sterile Water for Injection, USP, or 5% Dextrose Injection, USP, and subsequently diluted only with 5% Dextrose Injection, USP, to a final concentration of 1 mg/mL to 5 mg/mL.

Reconstitution: DALVANCE must be reconstituted under aseptic conditions, using 25 mL of either Sterile Water for Injection, USP, or 5% Dextrose Injection, USP, for each 500 mg vial. To avoid foaming, alternate between gentle swirling and inversion of the vial until its contents are completely dissolved. Do not shake. The reconstituted vial contains 20 mg/mL dalbavancin as a clear, colorless to yellow solution.

Reconstituted vials may be stored either refrigerated at 2 to 8 °C (36 to 46 °F), or at controlled room temperature 20 to 25 °C (68 to 77 °F). Do not freeze.

Dilution: Aseptically transfer the required dose of reconstituted dalbavancin solution from the vial(s) to an intravenous bag or bottle containing 5% Dextrose Injection, USP. The diluted solution must have a final dalbavancin concentration of 1 mg/mL to 5 mg/mL. Discard any unused portion of the reconstituted solution.

Once diluted into an intravenous bag or bottle as described above, DALVANCE may be stored either refrigerated at 2 to 8 °C (36 to 46 °F) or at a controlled room temperature of 20 to 25 °C (68 to 77 °F). Do not freeze.

The total time from reconstitution to dilution to administration should not exceed 48 hours.

Like all parenteral drug products, diluted DALVANCE should be inspected visually for particulate matter prior to infusion. If particulate matter is identified, do not use.

Administration: After reconstitution and dilution, DALVANCE is to be administered via intravenous infusion, using a total infusion time of 30 minutes.

Do not co-infuse DALVANCE with other medications or electrolytes. Saline-based infusion solutions may cause precipitation and should not be used. The compatibility of reconstituted DALVANCE with intravenous medications, additives, or substances other than 5% Dextrose Injection, USP has not been established.

If a common intravenous line is being used to administer other drugs in addition to DALVANCE, the line should be flushed before and after each DALVANCE infusion with 5% Dextrose Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

DALVANCE is supplied in clear glass vials containing sterile powder (white/off-white to pale yellow) equivalent to 500 mg of dalbavancin.

4 CONTRAINDICATIONS

DALVANCE is contraindicated in patients with known hypersensitivity to dalbavancin. No data are available on cross-reactivity between dalbavancin and other glycopeptides, including vancomycin.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity (anaphylactic) and skin reactions have been reported in patients treated with DALVANCE. If an allergic reaction occurs, treatment with DALVANCE should be discontinued. Before using DALVANCE, inquire carefully about previous hypersensitivity reactions to glycopeptides, and due to the possibility of cross-sensitivity, exercise caution in patients with a history of glycopeptide allergy *[see Patient Counseling Information (17)]*.

5.2 Infusion-Related Reactions

DALVANCE is administered via intravenous infusion, using a total infusion time of 30 minutes to minimize the risk of infusion-related reactions. Rapid intravenous infusions of DALVANCE can cause reactions that resemble "Red-Man Syndrome," including flushing of the upper body, urticaria, pruritus, and/or rash. Stopping or slowing the infusion may result in cessation of these reactions.

5.3 Hepatic Effects

In Phase 2 and 3 clinical trials, more DALVANCE than comparator-treated subjects with normal baseline transaminase levels had post-baseline alanine aminotransferase (ALT) elevation greater than 3 times the upper limit of normal (ULN). Overall, abnormalities in liver tests (ALT, AST, bilirubin) were reported with similar frequency in the DALVANCE and comparator arms *[see Adverse Reactions (6.1)]*.

5.4 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported in users of nearly all systemic antibacterial drugs, including DALVANCE, with severity ranging from mild diarrhea to fatal colitis. Treatment with antibacterial agents can alter the normal flora of the colon, and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible. Appropriate measures such as fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.5 Development of Drug-Resistant Bacteria

Prescribing DALVANCE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of DALVANCE cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

Adverse reactions were evaluated for 2473 patients treated with DALVANCE: 1778 patients were treated with DALVANCE in seven Phase 2/3 trials comparing DALVANCE to comparator antibacterial drugs and 695 patients were treated with DALVANCE in one Phase 3 trial comparing DALVANCE single and two-dose regimens. A causal relationship between study drug and adverse reactions was not always established. The median age of patients treated with DALVANCE was 48 years, ranging between 16 and 93 years. Patients treated with DALVANCE were predominantly male (59.5%) and White (81.2%).

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

Serious adverse reactions occurred in 121/2473 (4.9%) of patients treated with any regimen of DALVANCE. In the Phase 2/3 trials comparing DALVANCE to comparator, serious adverse reactions occurred in 109/1778 (6.1%) of patients in the DALVANCE group and 80/1224 (6.5%) of patients in the comparator group. In a Phase 3 trial comparing DALVANCE single and two-dose regimens, serious adverse reactions occurred in 7/349 (2.0%) of patients in the DALVANCE single dose group and 5/346 (1.4%) of patients in the DALVANCE two-dose group. DALVANCE was discontinued due to an adverse reaction in 64/2473 (2.6%) patients treated with any regimen of DALVANCE. In the Phase 2/3 trials comparing DALVANCE to comparator, DALVANCE was discontinued due to an adverse reaction in 53/1778 (3.0%) of patients in the DALVANCE group and 35/1224 (2.9%) of patients in the comparator group. In a Phase 3 trial comparing DALVANCE single and two-dose regimens, DALVANCE was discontinued due to an adverse reaction in 6/349 (1.7%) of patients in the DALVANCE single dose group and 5/346 (1.4%) of patients in the DALVANCE two-dose group.

Most Common Adverse Reactions

The most common adverse reactions in patients treated with DALVANCE were nausea (4.7%), headache (3.8%), and diarrhea (3.4%). The median duration of adverse reactions was 3.0 days in patients treated with DALVANCE. In the Phase 2/3 trials comparing DALVANCE to comparator, the median duration of adverse reactions was 3.0 days for patients in the DALVANCE group and 4.0 days in patients in the comparator group. In a Phase 3 trial comparing DALVANCE single and two-dose regimens, the median duration of adverse reactions was 3.0 days for patients in the DALVANCE single and two-dose group.

Table 2 lists selected adverse reactions occurring in 2% or more of patients treated with DALVANCE in Phase 2/3 clinical trials.

Table 2. Selected Adverse Reactions Occurring in ≥ 2% of Patients Receiving DALVANCE in Phase 2/3 Trials
(Number (%) of Patients)

Adverse Reactions	DALVANCE (N = 1778)	Comparator* (N = 1224)
Nausea	98 (5.5)	78 (6.4)
Vomiting	50 (2.8)	37 (3)
Diarrhea	79 (4.4)	72 (5.9)
Headache	83 (4.7)	59 (4.8)
Rash	48 (2.7)	30 (2.4)
Pruritus	38 (2.1)	41 (3.3)

* Comparators included linezolid, cefazolin, cephalexin, and vancomycin.

In the Phase 3 trial comparing the single and two-dose regimen of DALVANCE, the adverse reaction that occurred in 2% or more of patients treated with DALVANCE was nausea (3.4% in the DALVANCE single dose group and 2% in the DALVANCE two-dose group).

The following selected adverse reactions were reported in DALVANCE treated patients at a rate of less than 2% in these clinical trials:

Blood and lymphatic system disorders: anemia, hemorrhagic anemia, leucopenia, neutropenia, thrombocytopenia, petechiae, eosinophilia, thrombocytosis

Gastrointestinal disorders: gastrointestinal hemorrhage, melena, hematochezia, abdominal pain

General disorders and administration site conditions: infusion-related reactions

Hepatobiliary disorders: hepatotoxicity

Immune system disorders: anaphylactic reaction

Infections and infestations: *Clostridium difficile* colitis, oral candidiasis, vulvovaginal mycotic infection

Investigations: hepatic transaminases increased, blood alkaline phosphatase increased, international normalized ratio increased, blood lactate dehydrogenase increased, gamma-glutamyl transferase increased

Metabolism and nutrition disorders: hypoglycemia

Nervous system disorders: dizziness

Respiratory, thoracic and mediastinal disorders: bronchospasm

Skin and subcutaneous tissue disorders: rash, pruritus, urticaria

Vascular disorders: flushing, phlebitis, wound hemorrhage, spontaneous hematoma

Alanine Aminotransferase (ALT) Elevations

Among patients with normal baseline ALT levels treated with DALVANCE 17 (0.8%) had post-baseline ALT elevations greater than 3 times the upper limit of normal (ULN) including five subjects with post-baseline ALT values greater than 10 times ULN. Among patients with normal baseline ALT levels treated with non-DALVANCE comparators 2 (0.2%) had post-baseline ALT elevations greater than 3 times the upper limit of normal. Fifteen of the 17 patients treated with DALVANCE and one comparator patient had underlying conditions which could affect liver enzymes, including chronic viral hepatitis, history of alcohol abuse and metabolic syndrome. In addition, one DALVANCE-treated subject in a Phase 1 trial had post-baseline ALT elevations greater than 20 times ULN. ALT elevations were reversible in all subjects with follow-up assessments. No comparator-treated subject with normal baseline transaminases had post-baseline ALT elevation greater than 10 times ULN.

7 DRUG INTERACTIONS

7.1 Drug-Laboratory Test Interactions

Drug-laboratory test interactions have not been reported. DALVANCE at therapeutic concentrations does not artificially prolong prothrombin time (PT) or activated partial thromboplastin time (aPTT).

7.2 Drug-Drug Interactions

No clinical drug-drug interaction studies have been conducted with DALVANCE. There is minimal potential for drug-drug interactions between DALVANCE and cytochrome P450 (CYP450) substrates, inhibitors, or inducers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There have been no adequate and well-controlled studies with DALVANCE in pregnant women. DALVANCE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No treatment-related malformations or embryo-fetal toxicity were observed in pregnant rats or rabbits at clinically relevant exposures of dalbavancin. Treatment of pregnant rats with dalbavancin at 3.5 times the human dose on an exposure basis during early embryonic development and from implantation to the end of lactation resulted in delayed fetal maturation and increased fetal loss, respectively *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data

No evidence of embryo or fetal toxicity was found in the rat or rabbit at a dose of 15 mg/kg/day (1.2 and 0.7 times the human dose on an exposure basis, respectively). Delayed fetal maturation was observed in the rat at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis).

In a rat prenatal and postnatal development study, increased embryo lethality and increased offspring deaths during the first week post-partum were observed at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis).

8.2 Lactation

Risk Summary

It is not known whether dalbavancin or its metabolite is excreted in human milk; therefore, caution should be exercised when DALVANCE is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DALVANCE and any potential adverse effects on the breastfed child from DALVANCE or from the underlying maternal condition.

Data

Animal Data

Dalbavancin is excreted in the milk of lactating rats.

8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Of the 2473 patients treated with DALVANCE in Phase 2 and 3 clinical trials, 403 patients (16.3%) were 65 years of age or older. The efficacy and tolerability of DALVANCE were similar to comparator regardless of age. The pharmacokinetics of DALVANCE was not significantly altered with age; therefore, no dosage adjustment is necessary based on age alone.

DALVANCE is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

8.6 Renal Impairment

In patients with renal impairment whose known creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis, the recommended regimen for DALVANCE is 1125 mg, administered as a single dose, or 750 mg followed one week later by 375 mg. No dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis, and DALVANCE can be administered without regard to the timing of hemodialysis *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of DALVANCE is recommended for patients with mild hepatic impairment (Child-Pugh Class A). Caution should be exercised when prescribing DALVANCE to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) as no data are available to determine the appropriate dosing in these patients *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Specific information is not available on the treatment of overdose with DALVANCE, as dose-limiting toxicity has not been observed in clinical studies. In Phase 1 studies, healthy volunteers have been administered cumulative doses of up to 4500 mg over a period of up to 8 weeks, with no signs of toxicity or laboratory results of clinical concern.

Treatment of overdose with DALVANCE should consist of observation and general supportive measures. Although no information is available specifically regarding the use of hemodialysis to treat overdose, in a Phase 1 study in patients with renal impairment less than 6% of the recommended dalbavancin dose was removed *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

DALVANCE (dalbavancin) for injection is a lipoglycopeptide synthesized from a fermentation product of *Nonomuraea* species.

Dalbavancin is a mixture of five closely related active homologs (A_0, A_1, B_0, B_1, and B_2); the component B_0 is the major component of dalbavancin. The homologs share the same core structure and differ in the fatty acid side chain of the N-acylaminoglucuronic acid moiety (R_1) structure and/or the presence of an additional methyl group (R_2) on the terminal amino group (shown in the Figure 1 and Table 3 below).

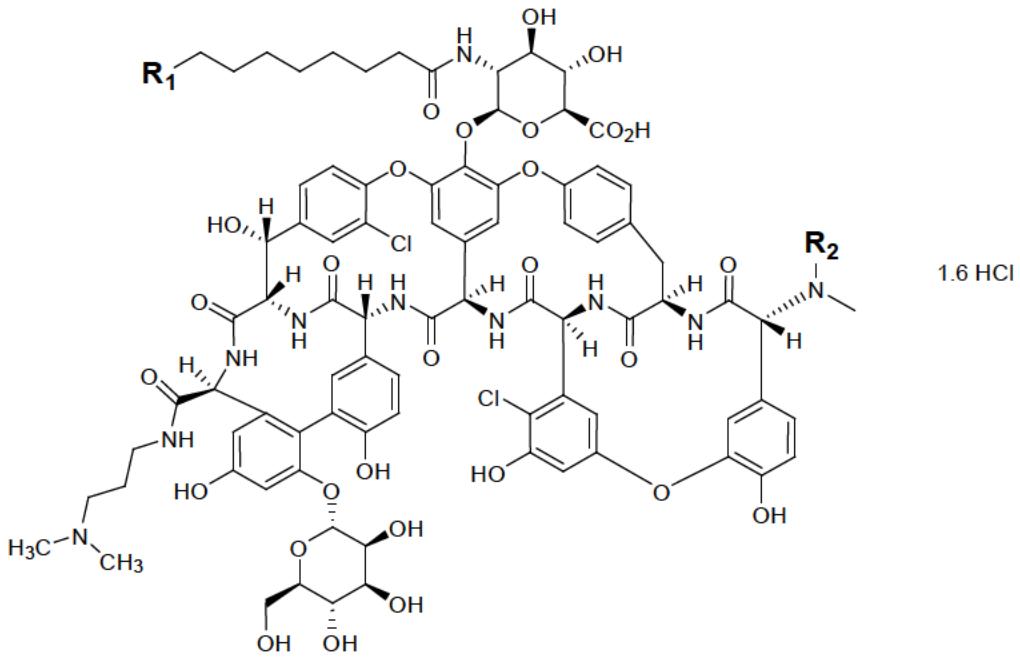


Figure 1. Dalbavancin Structural Formula

Table 3. Substitution Patterns for Dalbavancin API Homologs

Dalbavancin	R_1	R_2	Molecular Formula	Molecular Weight*
A_0	$CH(CH_3)_2$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7
A_1	$CH_2CH_2CH_3$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7
B_0	$CH_2CH(CH_3)_2$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7
B_1	$CH_2CH_2CH_2CH_3$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7
B_2	$CH_2CH(CH_3)_2$	CH_3	$C_{89}H_{102}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1830.7

*Anhydrous free base

The B_0 INN chemical name is: 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O-[2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl]-38-[[3-(dimethylamino)propyl] carbamoyl]-42-O-α-D-mannopyranosyl-15-N-methyl(ristomycin A aglycone) hydrochloride.

DALVANCE is supplied in clear glass vials as a sterile, lyophilized, preservative-free, white to off-white to pale yellow solid. Each vial contains dalbavancin HCl equivalent to 500 mg of dalbavancin as the free base, plus lactose monohydrate (129 mg) and mannitol (129 mg) as excipients. Sodium hydroxide or hydrochloric acid may be added to adjust the pH at the time of manufacture. The powder is to be reconstituted and further diluted for IV infusion *[see Dosage and Administration (2.3), How Supplied/Storage and Handling (16)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dalbavancin is an antibacterial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

The antibacterial activity of dalbavancin appears to best correlate with the ratio of area under the concentration-time curve to minimal inhibitory concentration (AUC/MIC) for *Staphylococcus aureus* based on animal models of infection. An exposure-response analysis of a single study in patients with complicated skin and skin structure infections supports the two-dose regimen *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*.

Cardiac Electrophysiology: In a randomized, positive- and placebo-controlled, thorough QT/QTc study, 200 healthy subjects received dalbavancin 1000 mg IV, dalbavancin 1500 mg IV, oral moxifloxacin 400 mg, or placebo. Neither dalbavancin 1000 mg nor dalbavancin 1500 mg had any clinically relevant adverse effect on cardiac repolarization.

12.3 Pharmacokinetics

Dalbavancin pharmacokinetic parameters have been characterized in healthy subjects, patients, and specific populations. Pharmacokinetic parameters following administration of single intravenous 1000 mg and 1500 mg doses were as shown in Table 4. The pharmacokinetics of dalbavancin can be described using a three-compartment model.

Table 4. Dalbavancin Pharmacokinetic Parameters in Healthy Subjects

Parameter	Single 1000 mg Dose	Single 1500 mg Dose
C_{max} (mg/L)	287 (13.9)[1]	423 (13.2)[4]
$AUC_{0\text{-}24}$ (mg•h/L)	3185 (12.8)[1]	4837 (13.7)[4]
$AUC_{0\text{-}Day7}$ (mg•h/L)	11160 (41.1)[2]	ND
$AUC_{0\text{-}inf}$ (mg•h/L)	23443 (40.9)[2]	ND
Terminal $t_{½}$ (h)	346 (16.5)[2,3]	ND
CL (L/h)	0.0513 (46.8)[2]	ND

All values are presented as mean (% coefficient of variation)
[1] Data from 50 healthy subjects.
[2] Data from 12 healthy subjects.
[3] Based upon population pharmacokinetic analyses of data from patients, the effective half-life is approximately 8.5 days (204 hours).
[4] Data from 49 healthy subjects.
Abbreviation: ND – not determined

In healthy subjects, dalbavancin $AUC_{0\text{-}24h}$ and C_{max} both increased proportionally to dose following single IV dalbavancin doses ranging from 140 mg to 1500 mg, indicating linear pharmacokinetics.

The mean plasma concentration-time profile for dalbavancin following the recommended two-dose regimen of 1000 mg followed one week later by 500 mg is shown in Figure 2.

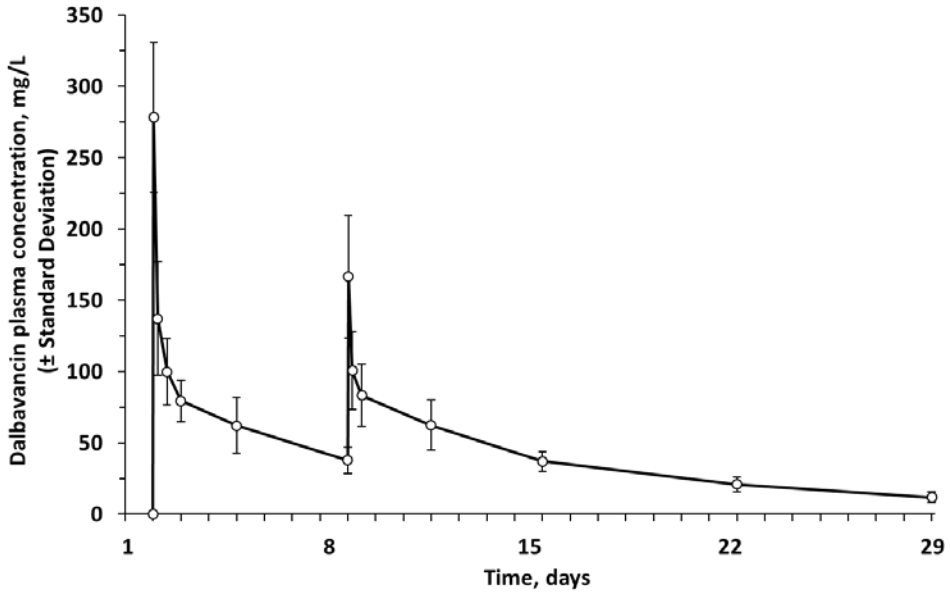


Figure 2. Mean (± standard deviation) dalbavancin plasma concentrations versus time in healthy subjects (n=10) following IV administration over 30 minutes of 1000 mg dalbavancin (Day 1) and 500 mg dalbavancin (Day 8).

No apparent accumulation of dalbavancin was observed following multiple IV infusions administered once weekly for up to eight weeks, with 1000 mg on Day 1 followed by up to seven weekly 500 mg doses, in healthy adults with normal renal function.

Distribution: Dalbavancin is reversibly bound to human plasma proteins, primarily to albumin. The plasma protein binding of dalbavancin is approximately 93% and is not altered as a function of drug concentration, renal impairment, or hepatic impairment. The mean concentrations of dalbavancin achieved in skin blister fluid remain above 30 mg/L up to 7 days (approximately 146 hours) post dose, following 1000 mg IV dalbavancin. The mean ratio of the $AUC_{0\text{-}144\ hrs}$ in skin blister fluid/$AUC_{0\text{-}144\ hrs}$ in plasma is 0.60 (range 0.44 to 0.64).

Metabolism: *In vitro* studies using human microsomal enzymes and hepatocytes indicate that dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes. A minor metabolite of dalbavancin (hydroxy-dalbavancin) has been observed in the urine of healthy subjects. Quantifiable concentrations of the hydroxy-dalbavancin metabolite have not been observed in human plasma (lower limit of quantitation = 0.4 µg/mL) *[see Drug Interactions (7.2)]*.

Excretion: Following administration of a single 1000 mg dose in healthy subjects, 20% of the dose was excreted in feces through 70 days post dose. An average of 33% of the administered dalbavancin dose was excreted in urine as unchanged dalbavancin and approximately 12% of the administered dose was excreted in urine as the metabolite hydroxy-dalbavancin through 42 days post dose.

Specific Populations

Renal Impairment: The pharmacokinetics of dalbavancin were evaluated in 28 subjects with varying degrees of renal impairment and in 15 matched control subjects with normal renal function.

Following a single dose of 500 mg or 1000 mg dalbavancin, the mean plasma clearance (CL_T) was reduced 11%, 35%, and 47% in subjects with mild (CL_{CR} 50 to 79 mL/min), moderate (CL_{CR} 30 to 49 mL/min), and severe (CL_{CR} less than 30 mL/min), renal impairment, respectively, compared to subjects with normal renal function. The clinical significance of the decrease in mean plasma CL_T, and the associated increase in $AUC_{0-\infty}$ noted in these pharmacokinetic studies of dalbavancin in subjects with severe renal impairment has not been established *[see Dosage and Administration (2.2), Use in Specific Populations (8.6)]*.

No dosage adjustment is necessary for patients with CL_{CR} greater than 30 mL/min or patients receiving hemodialysis. The recommended regimen for dalbavancin in patients with severe renal impairment who are not receiving regularly scheduled hemodialysis is 1125 mg, administered as a single dose, or 750 mg followed one week later by 375 mg.

Dalbavancin pharmacokinetic parameters in subjects with end-stage renal disease receiving regularly scheduled hemodialysis (three times/week) are similar to those observed in subjects with mild to moderate renal impairment, and less than 6% of an administered dose is removed after three hours of hemodialysis.
Therefore, no dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis, and dalbavancin may be administered without regard to the timing of hemodialysis in such patients *[see Dosage and Administration (2.1), Overdosage (10)]*.

Hepatic Impairment: The pharmacokinetics of dalbavancin were evaluated in 17 subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B or C) and compared to those in nine matched healthy subjects with normal hepatic function. The mean $AUC_{0-336\ hrs}$ was unchanged in subjects with mild hepatic impairment compared to subjects with normal hepatic function; however, the mean $AUC_{0-336\ hrs}$ decreased 28% and 31% in subjects with moderate and severe hepatic impairment respectively, compared to subjects with normal hepatic function. The clinical significance of the decreased $AUC_{0-336\ hrs}$ in subjects with moderate and severe hepatic function is unknown.

No dosage adjustment is recommended for patients with mild hepatic impairment. Caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic impairment as no data are available to determine the appropriate dosing.

Gender: Clinically significant gender-related differences in dalbavancin pharmacokinetics have not been observed either in healthy subjects or in patients with infections. No dosage adjustment is recommended based on gender.

Geriatric Patients: Clinically significant age-related differences in dalbavancin pharmacokinetics have not been observed in patients with infections. No dosage adjustment is recommended based solely on age.

Pediatric Patients: The pharmacokinetics of dalbavancin in pediatric populations <12 years of age have not been established.

Drug Interactions

Nonclinical studies demonstrated that dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes. In a population pharmacokinetic analysis, dalbavancin pharmacokinetics were not affected by co-administration with known CYP450 substrates, inducers or inhibitors, nor by individual medications including acetaminophen, aztreonam, fentanyl, metronidazole, furosemide, proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, lansoprazole), midazolam, and simvastatin.

12.4 Microbiology

Mechanism of Action
Dalbavancin, a semisynthetic lipoglycopeptide, interferes with cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking. Dalbavancin is bactericidal *in vitro* against *Staphylococcus aureus* and *Streptococcus pyogenes* at concentrations similar to those sustained throughout treatment in humans treated according to the recommended dosage regimen.

Mechanism of Resistance
The development of bacterial isolates resistant to dalbavancin has not been observed, either *in vitro*, in studies using serial passage, or in animal infection experiments.

Interaction with Other Antimicrobials
When tested *in vitro,* dalbavancin demonstrated synergistic interactions with oxacillin and did not demonstrate antagonistic or synergistic interactions with any of the following antibacterial agents of various classes: gentamicin, vancomycin, levofloxacin, clindamycin, quinupristin/dalfopristin, linezolid, aztreonam, rifampin or daptomycin. The clinical significance of these *in vitro* findings is unknown.

Dalbavancin has been shown to be active against the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

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

The following *in vitro* data are available, but their clinical significance is unknown. In addition, at least 90% of organisms in the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the dalbavancin susceptible breakpoint of 0.25 mcg/mL. However, the safety and efficacy of dalbavancin in treating clinical infections due to these bacteria have not been established in adequate well-controlled clinical trials.

Gram-positive bacteria

Enterococcus faecium (vancomycin-susceptible isolates only)

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

Dilution Techniques

Quantitative methods are used to determine minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method.[1,2] When determining dalbavancin MICs, polysorbate-80 (P-80), should be added at a final concentration of 0.002% to freshly prepared or frozen microtiter trays. The MIC values should be interpreted according to the criteria provided in Table 5.

Diffusion Techniques

Dalbavancin disks for diffusion susceptibility testing are not available. Disk diffusion is not a reliable method for determining the *in vitro* activity of dalbavancin.

Table 5. Susceptibility Test Interpretive Criteria for Dalbavancin

Pathogen	MIC (mcg/mL)[a]			Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.25	--	--	--	--	--
Streptococcus pyogenes, *Streptococcus agalactiae,* *Streptococcus dysgalactiae,* and *Streptococcus anginosus* group	≤ 0.25	--	--	--	--	--
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤ 0.25	--	--	--	--	--

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

A report of "Susceptible" indicates that the antibacterial agent is likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen.

Quality Control
Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.[1, 2] Standard dalbavancin powder should provide the following range of MIC values noted in Table 6.

Table 6. Acceptable MIC Quality Control Ranges for Dalbavancin

Quality Control Strain	MIC Range (µg/mL)
Staphylococcus aureus ATCC ®29213	0.03-0.12
Streptococcus pneumoniae ATCC ®49619[a]	0.008-0.03
Enterococcus faecalis ATCC ®29212	0.03-0.12

ATCC® = American Type Culture Collection
[a] This organism may be used for validation of susceptibility test results when testing *Streptococcus* species other than *S. pneumoniae*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to determine the carcinogenic potential of dalbavancin have not been conducted.

Dalbavancin was not genotoxic in a bacterial reverse mutation (Ames) assay, a mammalian HGPRT gene mutation assay, an *in vitro* chromosome aberration assay in Chinese Hamster Ovary cells, or an *in vivo* mouse micronucleus assay.

Impaired fertility in the rat was not observed at a dose of 15 mg/kg/day (1.2 times the human dose on an exposure basis). Reductions in male and female fertility and increased embryo resorptions occurred at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis), at which signs of parental toxicity were also observed**.**

13.2 Animal Toxicology and/or Pharmacology

Increases in serum levels of liver enzymes (ALT, AST), associated with microscopic findings in the liver were noted in toxicology studies in rats and dogs where dalbavancin was administered daily for 28 to 90 days. Hepatocellular necrosis was observed in dogs dosed at ≥10 mg/kg/day for longer than 2 months, i.e., at approximately 5 to 7 times the expected human dose on an exposure basis. Histiocytic vacuolation and hepatocyte necrosis were observed in rats dosed daily at 40 and 80 mg/kg/day, respectively, for 4 weeks, (approximately 3 and 6 times the expected human dose on an exposure basis, respectively). In addition, renal toxicity characterized by increases in serum BUN and creatinine and microscopic kidney findings was observed in rats and dogs at doses 5 to 7 times the expected human dose on an exposure basis. The relationship between these findings in the animal toxicology studies after 28 and 90 consecutive days of dosing to the indicated clinical dosing of 2 doses 7 days apart are unclear.

14 CLINICAL STUDIES

Acute Bacterial Skin and Skin Structure Infections:

DALVANCE Two-dose Regimen (1000 mg Day 1; 500 mg Day 8)

Adult patients with ABSSSI were enrolled in two Phase 3, randomized, double-blind, double-dummy clinical trials of similar design (Trial 1 and Trial 2). The Intent-to-Treat (ITT) population included 1,312 randomized patients. Patients were treated for two weeks with either a two-dose regimen of intravenous DALVANCE (1000 mg followed one week later by 500 mg) or intravenous vancomycin (1000 mg or 15 mg/kg every 12 hours, with the option to switch to oral linezolid after 3 days). DALVANCE-treated patients with creatinine clearance of less than 30 mL/min received 750 mg followed one week later by 375 mg. Approximately 5% of patients also received a protocol-specified empiric course of treatment with intravenous aztreonam for coverage of Gram-negative pathogens.

The specific infections in these trials included cellulitis (approximately 50% of patients across treatment groups), major abscess (approximately 30%), and wound infection (approximately 20%). The median lesion area at baseline was 341 cm^2. In addition to local signs and symptoms of infection, patients were also required to have at least one systemic sign of disease at baseline, defined as temperature 38°C or higher (approximately 85% of patients), white blood cell count greater than 12,000 cells/mm^3 (approximately 40%), or 10% or more band forms on white blood cell differential (approximately 23%). Across both trials, 59% of patients were from Eastern Europe and 36% of patients were from North America. Approximately 89% of patients were Caucasian and 58% were males. The mean age was 50 years and the mean body mass index was 29.1 kg/m^2.

The primary endpoint of these two ABSSSI trials was the clinical response rate where responders were defined as patients who had no increase from baseline in lesion area 48 to 72 hours after initiation of therapy, and had a temperature consistently at or below 37.6° C upon repeated measurement. Table 7 summarizes overall clinical response rates in these two ABSSSI trials using the pre-specified primary efficacy endpoint in the ITT population.

Table 7. Clinical Response Rates in ABSSSI Trials at 48-72 Hours after Initiation of Therapy[1,2]

	DALVANCE n/N (%)	Vancomycin/Linezolid n/N (%)	Difference (95% CI)[3]
Trial 1	240/288 (83.3)	233/285 (81.8)	1.5 (-4.6, 7.9)
Trial 2	285/371 (76.8)	288/368 (78.3)	-1.5 (-7.4, 4.6)

[1] There were 7 patients who did not receive treatment and were counted as non-responders: 6 DALVANCE patients (3 in each trial) and one vancomycin/linezolid patient in Trial 2.
[2] Patients who died or used non-study antibacterial therapy or had missing measurements were classified as non-responders.
[3] The 95% Confidence Interval (CI) is computed using the Miettinen and Nurminen approach, stratified by baseline fever status.

A key secondary endpoint in these two ABSSSI trials evaluated the percentage of ITT patients achieving a 20% or greater reduction in lesion area from baseline at 48-72 hours after initiation of therapy. Table 8 summarizes the findings for this endpoint in these two ABSSSI trials.

Table 8. Patients in ABSSSI Trials with Reduction in Lesion Area of 20% or Greater at 48-72 Hours after Initiation of Therapy[1,2]

	DALVANCE n/N (%)	Vancomycin/Linezolid n/N (%)	Difference (95% CI)[3]
Trial 1	259/288 (89.9)	259/285 (90.9)	-1.0 (-5.7, 4.0)
Trial 2	325/371 (87.6)	316/368 (85.9)	1.7 (-3.2, 6.7)

[1] There were 7 patients (as described in Table 7) who did not receive treatment and were counted as non-responders.
[2] Patients who died or used non-study antibacterial therapy or had missing measurements were classified as non-responders.
[3] The 95% CI is computed using the Miettinen and Nurminen approach, stratified by baseline fever status.

Another secondary endpoint in these two ABSSSI trials was the clinical success rate assessed at a follow-up visit occurring between Days 26 to 30. Clinical Success at this visit was defined as having a decrease in lesion size (both length and width measurements), a temperature of 37.6° C or lower, and meeting pre-specified criteria for local signs: purulent discharge and drainage absent or mild and improved from baseline, heat/warmth & fluctuance absent, swelling/induration & tenderness to palpation absent or mild.

Table 9 summarizes clinical success rates at a follow-up visit for the ITT and clinically evaluable population in these two ABSSSI trials. Note that there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at the follow-up visits. Therefore, comparisons of DALVANCE to vancomycin/linezolid based on clinical success rates at these visits cannot be utilized to establish non-inferiority.

Table 9. Clinical Success Rates in ABSSSI Trials at Follow-Up (Day 26 to 30)[1,2]

	DALVANCE n/N (%)	Vancomycin/Linezolid n/N (%)	Difference (95% CI)[3]
Trial 1			
ITT	241/288 (83.7%)	251/285 (88.1%)	-4.4% (-10.1, 1.4)
CE	212/226 (93.8%)	220/229 (96.1%)	-2.3% (-6.6, 2.0)
Trial 2			
ITT	327/371 (88.1%)	311/368 (84.5%)	3.6% (-1.3, 8.7)
CE	283/294 (96.3%)	257/272 (94.5%)	1.8% (-1.8, 5.6)

[1] There were 7 patients (as described in Table 7) who did not receive treatment and were counted as failures in the analysis.
[2] Patients who died, used non-study antibacterial therapy, or had an unplanned surgical intervention 72 hours after the start of therapy were classified as Clinical Failures.
[3] The 95% CI is computed using the Miettinen and Nurminen approach, stratified by baseline fever status.

Table 10 shows outcomes in patients with an identified baseline pathogen, using pooled data from Trials 1 and 2 in the microbiological ITT (microITT) population. The outcomes shown in the table are clinical response rates at 48 to 72 hours and clinical success rates at follow-up (Day 26 to 30), as defined above.

Table 10. Outcomes by Baseline Pathogen (Trial 1, 2; MicroITT) [1]

	Early Clinical Response at 48-72 hours					
	Early Responder[2]		≥ 20% reduction in lesion size		Clinical Success at Day 26 to 30	
Pathogen	**DALVANCE n/N (%)**	**Comparator n/N (%)**	**DALVANCE n/N (%)**	**Comparator n/N (%)**	**DALVANCE n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	206/257 (80.2)	219/256 (85.5)	239/257 (93.0)	232/256 (90.6)	217/257 (84.4)	229/256 (89.5)
Methicillin-susceptible	134/167 (80.2)	163/189 (86.2)	156/167 (93.4)	173/189 (91.5)	142/167 (85.0)	171/189 (90.5)
Methicillin-resistant	72/90 (80.0)	56/67 (83.6)	83/90 (92.2)	59/67 (88.1)	75/90 (83.3)	57/67 (85.1)
Streptococcus agalactiae	6/12 (50.0)	11/14 (78.6)	10/12 (83.3)	10/14 (71.4)	10/12 (83.3)	11/14 (78.6)
Streptococcus pyogenes	28/37 (75.7)	24/36 (66.7)	32/37 (86.5)	27/36 (75.0)	33/37 (89.2)	32/36 (88.9)
Streptococcus anginosus group	18/22 (81.8)	23/ 25 (92.0)	21/22 (95.5)	25/25 (100.0)	21/22 (95.5)	23/25 (92.0)
Enterococcus faecalis	8/12 (66.7)	10/13 (76.9)	12/12 (100.0)	12/13 (92.3)	12/12 (100.0)	11/13 (84.6)

All DALVANCE dosing regimens in Trials 1 and 2 consisted of two doses.

[1] There were 2 patients in the DALVANCE arm with methicillin-susceptible *S. aureus* at baseline who did not receive treatment and were counted as non-responders/failures.

[2] Early Responders are patients who had no increase from baseline in lesion area 48 to 72 hours after initiation of therapy, and had a temperature consistently at or below 37.6° C upon repeated measurement.

DALVANCE 1500 mg Single Dose Regimen

Adult patients with ABSSSI were enrolled in a Phase 3, double-blind, clinical trial. The ITT population included 698 patients who were randomized to DALVANCE treatment with either a single 1500 mg dose or a two-dose regimen of 1000 mg followed one week later by 500 mg (Trial 3). Patients with creatinine clearance less than 30 mL/min had their dose adjusted (Section 2.2). Approximately 5% of patients also received a protocol-specified empiric course of treatment with intravenous aztreonam for coverage of Gram-negative pathogens. The specific infections and other patient characteristics in this trial were similar to those described above for previous ABSSSI trials.

The primary endpoint in this ABSSSI trial was the clinical response rate where responders were defined as patients who had at least a 20% decrease from baseline in lesion area 48 to 72 hours after randomization without receiving any rescue antibacterial therapy. The secondary endpoint was the clinical success rate at a follow-up visit occurring between Days 26 and 30, with clinical success defined as having at least a 90% decrease from baseline in lesion size, a temperature of 37.6° C or lower, and meeting pre-specified criteria for local signs: purulent discharge and drainage absent or mild and improved from baseline (for patients with wound infections), heat/warmth and fluctuance absent, swelling/induration and tenderness to palpation absent or mild. Table 11 summarizes results for these two endpoints in the ITT population. Note that there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at the follow-up visit. Therefore, comparisons between treatment groups based on clinical success rates at this visit cannot be utilized to establish non-inferiority.

Table 11. Primary and Secondary Efficacy Results in ABSSSI Patients (Trial 3) [1,2]

	DALVANCE, n/N (%)		
	Single Dose (1500 mg)	**Two doses (1000 mg Day 1/500 mg Day 8)**	**Difference (95% CI)[3]**
Clinical Responders at 48-72 Hours (ITT)	284/349 (81.4)	294/349 (84.2)	-2.9 (-8.5, 2.8)
Clinical Success at Day 26-30 (ITT)	295/349 (84.5)	297/349 (85.1)	-0.6 (-6.0, 4.8)
Clinical Success at Day 26-30 (CE)	250/271 (92.3)	247/267 (92.5)	-0.3 (-4.9, 4.4)

[1] There were 3 patients in the two-dose group who did not receive treatment and were counted as non-responders.
[2] Patients who died or used non-study antibacterial therapy or had missing measurements were classified as non-responders.
[3] The 95% Confidence Interval (CI) is computed using the Miettinen and Nurminen approach.
Abbreviations: ITT-intent to treat; CE-clinically evaluable

Table 12 shows outcomes in patients with an identified baseline pathogen from Trial 3 in the microbiological ITT (microITT) population. The outcomes shown in the table are clinical response rates at 48 to 72 hours and clinical success rates at follow-up (Day 26 to 30), as defined above.

Table 12. Outcomes by Baseline Pathogen (Trial 3; MicroITT)

	Early Clinical Response at 48-72 hours			
	≥ 20% reduction in lesion size		**Clinical Success at Day 26 to 30**	
Pathogen	**Single dose (1500 mg) n/N (%)**	**Two doses (1000 mg Day 1/ 500 mg Day 8) n/N (%)**	**Single dose (1500 mg) n/N (%)**	**Two doses (1000 mg Day 1/ 500 mg Day 8) n/N (%)**
Staphylococcus aureus	123/139 (88.5)	133/156 (85.3)	124/139 (89.2)	140/156 (89.7)
Methicillin-susceptible	92/103 (89.3)	89/96 (89.6)	93/103 (90.3)	86/96 (89.6)
Methicillin-resistant	31/36 (86.1)	48/61 (78.7)	31/36 (86.1)	55/61 (90.2)
Streptococcus agalactiae	6/6(100.0)	4/6 (66.7)	5/6 (83.3)	5/6 (83.3)
Streptococcus anginosus group	31/33 (93.9)	19/19 (100.0)	29/33 (87.9)	17/19 (89.5)
Streptococcus pyogenes	14/14 (100.0)	18/22 (81.8)	13/14 (92.9)	19/22 (86.4)
Enterococcus faecalis	4/4 (100.0)	8/10 (80.0)	4/4 (100.0)	9/10 (90.0)

In Trials 1, 2, and 3, all patients had blood cultures obtained at baseline. A total of 40 ABSSSI patients who received DALVANCE had bacteremia at baseline caused by one or more of the following bacteria: 26 *S. aureus* (21 MSSA and 5 MRSA), 6 *S. agalactiae*, 7 *S. pyogenes*, 2 *S. anginosus* group, and 1 *E. faecalis*. In patients who received DALVANCE, a total of 34/40 (85%) were clinical responders at 48-72 hours and 32/40 (80%) were clinical successes at Day 26 to 30.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antibiotic Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Tenth Edition. CLSI document M07-A10. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. CLSI document M100-S25 Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

16 HOW SUPPLIED/STORAGE AND HANDLING

DALVANCE (dalbavancin) for injection is supplied in the following packaging configuration:

500 mg/vial: package of 1 (NDC 57970-100-01)

Unreconstituted DALVANCE (dalbavancin) for injection should be stored at 25ºC (77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Patients should be advised that allergic reactions, including serious allergic reactions, could occur, and that serious allergic reactions require immediate treatment. Patients should inform their healthcare provider about any previous hypersensitivity reactions to DALVANCE, or other glycopeptides.

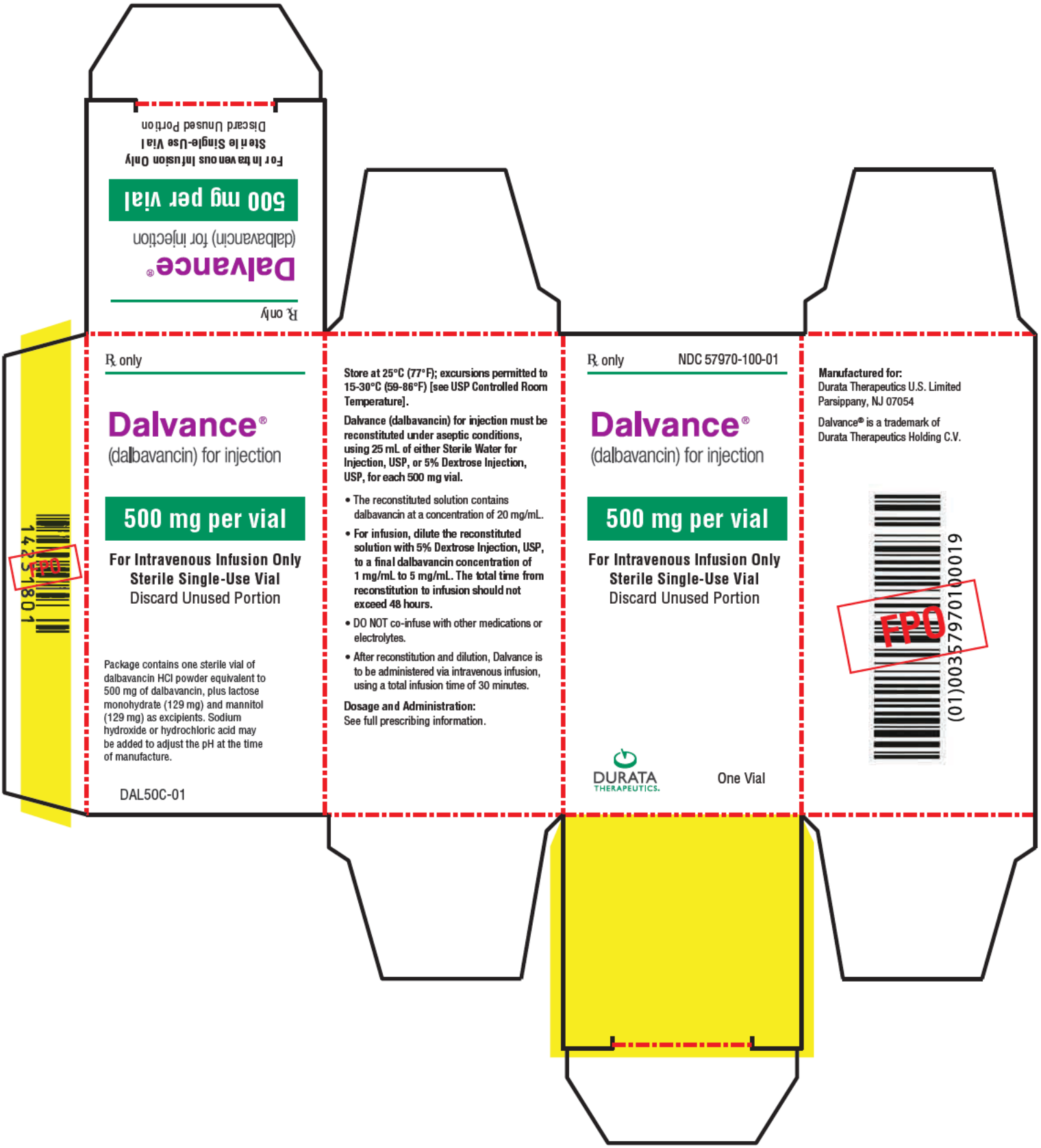
Patients should be counseled that antibacterial drugs including DALVANCE should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DALVANCE is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DALVANCE and other antibacterial drugs in the future.

Patients should be advised that diarrhea is a common problem caused by antibacterial drugs and usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, patients should contact their healthcare provider.

Manufactured for: Durata Therapeutics U.S. Limited
Parsippany, NJ 07054

US Patent Numbers: Available online at http://www.duratatherapeutics.com/products/product-patents

DALVANCE is a registered trademark of Durata Therapeutics Holding C.V.


For Intravenous Infusion Only
Sterile Single-Use Vial
Discard Unused Portion
500 mg per vial
Dalvance®
(dalbavancin) for injection
℞ only
℞ only
Dalvance®
(dalbavancin) for injection
500 mg per vial
For Intravenous Infusion Only
Sterile Single-Use Vial
Discard Unused Portion
Package contains one sterile vial of dalbavancin HCl powder equivalent to 500 mg of dalbavancin, plus lactose monohydrate (129 mg) and mannitol (129 mg) as excipients. Sodium hydroxide or hydrochloric acid may be added to adjust the pH at the time of manufacture.
DAL50C-01
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Dalvance (dalbavancin) for injection must be reconstituted under aseptic conditions, using 25 mL of either Sterile Water for Injection, USP, or 5% Dextrose Injection, USP, for each 500 mg vial.
• The reconstituted solution contains dalbavancin at a concentration of 20 mg/mL.
• For infusion, dilute the reconstituted solution with 5% Dextrose Injection, USP, to a final dalbavancin concentration of 1 mg/mL to 5 mg/mL. The total time from reconstitution to infusion should not exceed 48 hours.
• DO NOT co-infuse with other medications or electrolytes.
• After reconstitution and dilution, Dalvance is to be administered via intravenous infusion, using a total infusion time of 30 minutes.
Dosage and Administration:
See full prescribing information.
℞ only NDC 57970-100-01
Dalvance®
(dalbavancin) for injection
500 mg per vial
For Intravenous Infusion Only
Sterile Single-Use Vial
Discard Unused Portion
DURATA THERAPEUTICS.
One Vial
Manufactured for:
Durata Therapeutics U.S. Limited
Parsippany, NJ 07054
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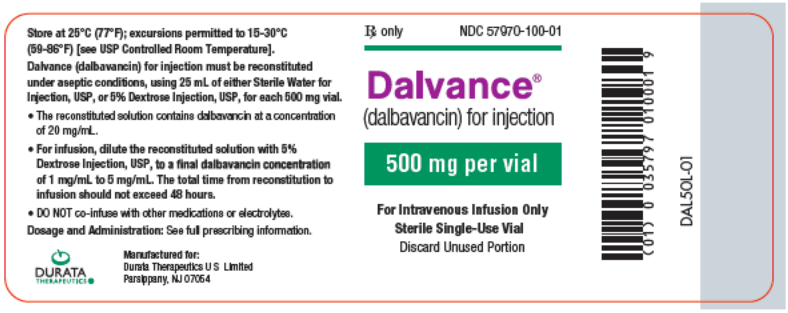
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• For infusion, dilute the reconstituted solution with 5% Dextrose Injection, USP, to a final dalbavancin concentration of 1 mg/mL to 5 mg/mL. The total time from reconstitution to infusion should not exceed 48 hours.
• DO NOT co-infuse with other medications or electrolytes.
Dosage and Administration: See full prescribing information.
DURATA THERAPEUTICS
Manufactured for:
Durata Therapeutics U S Limited
Parsippany, NJ 07054
℞ only
NDC 57970-100-01
Dalvance®
(dalbavancin) for injection
500 mg per vial
For Intravenous Infusion Only
Sterile Single-Use Vial
Discard Unused Portion
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DAL50L-01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

OFFICER/EMPLOYEE LIST

NDA 21-883/S-003

The following employees of FDA participated in the decision to approve this application and consented to be identified on this list:

1. ***Janice Pohlman***
2. ***Adam George***
3. ***Abimbola Adebowale***
4. ***Christopher Kadoorie***
5. ***Wendelyn Schmidt***
6. ***Seong Jang***
7. ***Sumathi Nambiar***
8. ***Rama Kapoor***
9. ***John Metcalfe***
10. ***Yang He***
11. ***Kalavati Suvarna***
12. ***Dmitri Iarikov***

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

DIVISION DIRECTOR MEMO

Division Director Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Memo
NDA # s	21883/S-003
Applicant Name	Durata Therapeutics International, B.V.
Date of Submission	July 20, 2015
PDUFA Goal Date	January 20, 2016
Established (USAN) Name	Dalbavancin
Trade Name	DALVANCE
Dosage Forms / Strength	Lyophilized Powder for Injection / 500 mg
Proposed Indications	Treatment of Acute Bacterial Skin and Skin Structure Infections
Recommended Action:	Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Cross-Discipline Team Leader Review	Dmitiri Iarikov MD PhD
Pharmacology Toxicology Review	Terry Miller PhD
Medical Officer Review	Rama Kapoor MD
Statistical Review	Christopher Kadoorie PhD
Microbiology Review	Kalavati Suvarna PhD
Clinical Pharmacology Review	Yang He PhD
Product Quality Review	Dorota Matecka PhD
Office of Scientific Investigations	John Lee MD
Division of Medication Error Prevention and Analysis	Jacqueline Sheppard Pharm D
Office of Prescription Drug Promotion	Adam George Pharm D

1.0 Introduction

Dalbavancin is a lipoglycopeptide antibacterial drug that was approved on May 23, 2014 for the treatment of adults with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) caused by susceptible isolates of *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group. The currently approved dosing regimen is intravenous administration of 1000 mg on day 1 followed by 500 mg a week later with dose adjusted in patients with creatinine clearance less than 30 mL/min and not receiving regularly scheduled hemodialysis.

2.0 Background

The approval of dalbavancin was based on two Phase 3 randomized double-blind trials in adults with ABSSSI which demonstrated that the 2-dose regimen of dalbavancin was noninferior to the comparator (intravenous vancomycin, with the option to switch to oral linezolid).

This supplemental NDA was submitted to support a single 1500 mg dose of dalbavancin for the treatment of ABSSSI. To support the single-dose regimen, the Applicant conducted a randomized double-blind trial comparing the single-dose regimen with the 2-dose regimen (Study DUR001-303). As dalbavancin for injection has Qualified Infectious Disease Product (QIDP) designation for ABSSSI, the application received a priority review.

The review team has completed their reviews of this supplemental application. For a detailed discussion of NDA 21883/S-003, please refer to the discipline specific reviews and the Cross-Discipline Team Leader review.

3.0 Product Quality

The only CMC change associated with this efficacy supplement includes lowering a limit for endotoxins (from NMT 0.35 EU/mg to NMT 0.23 EU/mg) in the drug product specification. Dr. Matecka notes that the CMC information provided in the supplement in support of this revision was acceptable to the Product Quality Microbiology Reviewer Dr. Daniel Schu, PhD. Dr. Matecka also notes that the Applicant's request for categorical exclusion from environmental assessment is acceptable and recommends approval of S-003.

In a previous supplement (S-002), the Applicant had proposed revising the carton and container labeling to use the term single-use rather than single-dose given that a single-dose regimen was being developed. This supplement was approved on December 18, 2015. The Office of Pharmaceutical Quality (OPQ) review filed for S-002 noted that the issue was still under discussion and will be addressed during the review of S-003.

This issue was discussed extensively with Division of Medication Error Prevention and Analysis and OPQ including members of the Office of Policy for Pharmaceutical Quality (OPPQ). Please see Dr. Matecka's review for details. While draft FDA guidance recommends the term single-dose to label vials designed for use in a single patient as a single infusion, there is concern that with the approval of the single-dose regimen the use of the term single-dose for the carton and container labeling may result in dosing errors.[1] Dalbavancin is available in 500 mg vials and the proposed 1500 mg single-dose regimen (or 1125 mg in patients with creatinine clearance less than 30 mL/min) requires three vials. The single 500 mg vial will be an adequate dose only as part of the two-dose regimen (1000 mg on day 1 and 500 mg on day 8 and 750 mg on day 1 and 375 mg on day 8 in patients with creatinine clearance less than 30 mL/min respectively). Labeling of a vial as a single-dose may imply that one vial constitutes the full single-dose regimen and result in administering a sub-therapeutic dose or in some instances a higher dose. Similar concerns related to use of the term single-dose in container labeling have been raised in comments submitted to the docket for the draft guidance.[2]

Given the availability of a single-dose regimen and the potentially deleterious outcomes should patients with ABSSSI be under-dosed, the term single-use rather than single-dose will be included in the carton and container labeling. While this is a deviation from the policy noted in the draft guidance, the unique aspects of the dosing regimens for this drug, the potential for adverse outcomes if patients are under-dosed and the fact that similar concerns have been raised in the comments to the guidance, it seems appropriate to retain the term single-use for this product at this time. Once the comments to the docket are reviewed and the draft guidance is finalized, the labeling can be revised as needed. Also, once the product is used as a single-dose regimen and if subsequent reports of confusion or medication errors are noted with this particular product post-approval, further modification of labeling may be needed.

4.0 Pharmacology/Toxicology

Dr. Terry Miller, PhD is the pharmacology/toxicology reviewer for this sNDA.

No new nonclinical studies were conducted to support the proposed single-dose regimen. The package insert was revised to be compliant with the requirements of the Pregnancy, Lactation, Labeling Rule (PLLR). Dr. Miller has provided labeling recommendations to be consistent with the PLLR requirements and these have been incorporated in labeling. Dr. Miller recommends

[1] Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, Guidance for Industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

[2] http://www.regulations.gov/#!docketBrowser;rpp=25;po=0;dct=PS;D=FDA-2015-D-3438; accessed January 17, 2015.

approval of this sNDA from a pharmacology/toxicology perspective and I agree with his assessment.

5.0 Clinical Microbiology

The clinical microbiology reviewer for this sNDA is Kalavati Suvarna, PhD.

In surveillance studies, the MIC against *S. aureus* ranged from ≤0.03 to 0.25 mcg/mL for methicillin-susceptible *S. aureus* (MSSA) and from ≤0.03 to 0.5 mcg/mL for methicillin-resistant *S. aureus* (MRSA). Approximately 0.3% of isolates had MIC values greater than the current susceptible breakpoint of ≤ 0.12 mcg/mL. The MIC90 for *S. pyogenes*, *S. agalactiae* and *S. dysgalactiae* was ≤0.03 mcg/mL, 0.06 mcg/mL, and <0.03 mcg/mL respectively. Approximately 1% of *S. agalactiae* isolates had MIC values greater than the current susceptible breakpoint of ≤ 0.12 mcg/mL. Surveillance data from 2014 showed that the highest dalbavancin MIC for *E. faecalis* was 0.25 mcg/mL. The highest dalbavancin MIC in surveillance data from 2002-2013 for *E. faecalis* was >4.0 mcg/mL. The MIC distribution for *Enterococcus* species is bimodal with MIC90s for vancomycin-susceptible *E. faecalis and E. faecium* of 0.12 mcg/mL and ≥ 4.0 mcg/mL for vancomycin-resistant *E. faecalis* and *E. faecium*.

The Applicant submitted two studies in which dalbavancin MICs against gram-positive clinical isolates from the surveillance program were retested.

In study 15-DUR-02, isolates of *S. aureus* and *Streptococci* were retested to confirm the dalbavancin nonsusceptible results obtained in the surveillance program from 2011- 2013 (0.18% of isolates had dalbavancin MIC > 0.12 mcg/mL). Variability in dalbavancin MICs were observed both at the lower end of the MIC distribution and with dalbavancin non-susceptible isolates of *S. aureus* and streptococci. The initial dalbavancin MIC against *S. aureus* isolates selected for retesting was 0.25 (b) (4) mcg/mL. Among the *S. aureus* isolates, 20.5% (8/39) showed reproducible non-susceptible MIC results (i.e. ≥ 0.25 mcg/mL) and the remainder (79.5%; 31/39) had dalbavancin MIC of 0.03 – 0.12 mcg/mL. The initial dalbavancin MIC for all streptococcal isolates was 0.25 mcg/mL. The dalbavancin MIC was not reproducible against these isolates (32 isolates at 0.015 mcg/mL; 5 isolates at 0.03 mcg/mL; and 2 isolates at 0.06 mcg/mL).

In study 15-DUR-05, dalbavancin MIC was retested for isolates at the lower end of the MIC distribution in the 2014 surveillance program. On retesting all isolates with initial MIC values at the lower end of the MIC distribution had MICs closer to the respective modal MIC upon retesting with the exception of one *S. pyogenes* isolate. The reasons for the variability in dalbavancin MICs upon retesting are not known.

All baseline isolates in study DUR001-303 had dalbavancin MICs of ≤0.12 mcg/mL. The dalbavancin MIC range for baseline isolates in the three Phase 3 trials ranged from 0.001 to 0.25 mcg/mL.

The Applicant has proposed to include *S. dysgalactiae,* (b) (4) and *E. faecalis* (vancomycin-susceptible isolates only) in the Indications and Usage section (1.1) and in the first list of microorganisms in the Microbiology subsection (12.4) of the package insert. Dr. Suvarna agrees with the inclusion of *S. dysgalactiae* and *E. faecalis* (vancomycin-susceptible isolates only) based on data from the pooled Phase 3 trials and that the single-dose regimen is acceptable from a pharmacokinetic standpoint. (b) (4) will not be included in the Indications and Usage section or in the first list in the Microbiology subsection as it is not considered a relevant pathogen in ABSSSI.

Dr. Suvarna recommends approval of the sNDA. I agree with Dr. Suvarna's assessment.

6.0 Clinical Pharmacology

The clinical pharmacology reviewer for this sNDA is Yang He, PhD. Clinical pharmacology studies submitted in this sNDA include an updated population pharmacokinetic (PK) analysis, a PK/PD study in a neutropenic mouse model, and an in vitro study evaluating cytochrome P450 induction potential of dalbavancin in human hepatocytes.

The Applicant proposed a single dose of (b) (4) mg in patients with severe renal impairment (creatinine clearance < 30 mL/min and not on hemodialysis). Based on the modeling and simulation results, the single (b) (4) dose is predicted to provide a mean dalbavancin AUC 0-15 days of 17,085 mcg/mL·hr in patients with severe renal impairment, which is 12.4% lower than the mean AUC 0-15 days of 19,519 mcg/mL·hr after a single 1500 mg dose in patients with normal renal function. The recommended two-dose regimen of dalbavancin (750 mg on Day 1 and 375 mg a week later) provides a total dose of 1125 mg. To be consistent with the total dose of the approved two-dose regimen and given the dose-proportional and linear PK properties of dalbavancin, Dr. He recommends a single 1125 mg dose of dalbavancin for patients with severe renal impairment. This dose would produce almost identical mean AUC over 7 and 15 days as that seen with the single 1500 mg dose in subjects with normal renal function, and the Cmax will be within the range of PK variability. The labeled dosing regimens will be as follows:

Table 1: Dosing Regimens

Estimated CrCl	Single Dose Regimen	Two-Dose Regimen
≥ 30 mL/min or on regular hemodialysis	1500 mg	1000 mg followed one week later by 500 mg
< 30 mL/min and not on regular hemodialysis	1125 mg	750 mg followed one week later by 375 mg

The Applicant proposed a new qualified bioanalytical method (LC-MS/MS) for the analysis of dalbavancin in mouse plasma samples. In the new mouse PK/PD study, dalbavancin concentrations were assayed with this method, while in the previous animal PK/PD study, a bioassay method was used to assess dalbavancin concentrations. At comparable dose levels, dalbavancin concentrations in plasma determined in the new study were lower than those determined in the previous animal study. The concentrations determined by the new method are considered more reliable because this method measured the actual dalbavancin levels while the bioassay might have measured overall antimicrobial activity, which was then transformed into the corresponding dalbavancin concentration.

The potential of dalbavancin to induce human cytochrome P450 (CYP) isozymes was assessed using cryopreserved plateable human hepatocytes focusing on three major inducible drug metabolizing enzymes, i.e., CYP 1A2, 2B6, and 3A4. Dalbavancin at concentrations of up to 1000 mcg/mL showed no induction potential for CYP1A2. Due to the effect of Tween-80 and Captisol on the induction of CYP 2B6 and 3A4, the induction potential of dalbavancin on these two enzymes could not be adequately evaluated in this study.

Susceptibility Test Interpretive Criteria:

The Applicant has not used the exposure-response (ER) analysis to support the susceptibility test interpretive criteria as there is a flat relationship between the PK/PD index (AUC/MIC) and clinical efficacy. The Applicant performed target attainment analysis using AUC/MIC target value obtained from a new animal dose fractionation study and indicated that the nonclinical PK/PD cutoff would be able to support a susceptible breakpoint up to 2 mcg/mL. Based on this nonclinical PK/PD cutoff information, the Applicant proposed to increase the current susceptible breakpoint from 0.12 to (b) (4) mcg/mL against *S. aureus*. Overall, the clinical microbiology data support a susceptible breakpoint of ≤0.12 mcg/mL for *S. aureus* (including methicillin-resistant isolates), *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* group, *E. faecalis* (vancomycin-susceptible isolates only) based on in vitro MIC distributions of isolates from clinical studies and surveillance studies. In the all three Phase 3 trials combined, the highest MIC for *S. aureus* was 0.25 mg/mL isolated from a total of two patients. Clinical success at 72 hours was 50% in these patients and both patients were successes at the end of treatment. Based on the

available microbiology, nonclinical, and clinical data, Dr. He recommends a susceptible breakpoint of 0.25 mcg/mL for the target pathogens. Dr. Suvarna notes in an addendum dated January 19, 2016 that a susceptible breakpoint of 0.25 mcg/mL is acceptable for the bacteria listed in the Indication and Usage section.

Dr. He recommends approval of the sNDA and I agree with his recommendation.

7.0 Clinical Efficacy and Safety

The clinical reviewer for this sNDA is Rama Kapoor, MD and the statistical reviewer is Christopher Kadoorie, PhD.

Efficacy

The efficacy of a single-dose regimen of dalbavancin for the treatment of ABSSSI was evaluated in a Phase 3 randomized, double-blind, noninferiority trial (Study DUR001-303) comparing a single-dose of dalbavancin with the approved two-dose regimen. Patients in the single-dose group received dalbavancin 1500 mg on day 1 followed by placebo on day 8. Patients in the two-dose group received dalbavancin 1000 mg on day 1 followed by dalbavancin 500 mg on day 8. In patients with CrCl < 30 mL/min and not receiving hemodialysis, the dalbavancin dose was 1000 mg in the single-dose group and 750 mg on day 1 followed by 375 mg on day 8 in the two-dose group.

The enrollment criteria in the trial were consistent with those recommended in the guidance on developing drugs for treatment of ABSSSI.[3] Enrollment of patients with major abscesses was capped at 30%.

The primary efficacy endpoint was clinical response at 48 to 72 hours after the initiation of study drug in the intent-to-treat (ITT) population. Clinical response was defined as a decrease of ≥ 20% in lesion area, patient is alive and has received no rescue therapy for ABSSSI. Patients who had missing lesion measurements at baseline or in the 48-72 hours after the initiation of study drug were classified as non-responders. The ITT population included all randomized patients regardless of whether or not they received study drug. The pre-defined noninferiority margin was 10%.

Key secondary efficacy endpoints included clinical success at the end of treatment (day 14-15) and final (day 28) visits. As one of the previously conducted Phase 3 trials showed a lower clinical success rate at day 26 to 30 in the dalbavancin arm, for Study DUR001-003 the Division

[3] Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment, October 2013. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071185.pdf

had pre-specified that at the day 28 visit, the lower limit of the 95% confidence interval (CI) for the difference in clinical success in the ITT population must be no less than -15% in order for the trial to be considered successful.

Clinical success at the End of Treatment (EOT) visit was defined as a decrease in lesion area by ≥ 80 % from baseline, the patient's temperature ≤ 37.6°C, and all local signs of infection no worse than mild. Clinical success at the final visit was defined as a decrease in lesion area by ≥ 90% from baseline, temperature ≤ 37.6°C, tenderness to palpation and swelling no worse than mild and absent fluctuance and warmth.

A total of 698 subjects were randomized with 349 subjects included in each treatment group. Demographic and baseline characteristics were similar between the two treatment groups; mean age was 48 years, ~58% of subjects were males, and ~89% were White. Approximately 45% were enrolled in the United States. The most common infection type was cellulitis (~47%) followed by wound infection (~26%) and major abscess (~26%).

The median lesion area of cellulitis was 376 cm^2 and 345 cm^2 in the single- and two-dose group, respectively. *S. aureus* was the most commonly isolated bacterium; 17% and 24.5% in the single- and two-dose group, respectively were MRSA. The results of the primary efficacy analysis are shown in Table 2.

Table 2: Efficacy Analysis in the ITT Population

	Single-Dose Group n/N (%)	**Two-Dose Group n/N (%)**	**Treatment difference (95% CI)**
Clinical Response at 48-72 hours	284/349 (81.4)	294/349 (84.2)	-2.9 (-8.5, 2.8)
Clinical Success at EOT	293/349 (84.0)	296/349 (84.8)	-0.9 (-6.3, 4.6)
Clinical Success at FV	295/349 (84.5)	297/349 (85.1)	-0.6 (-6.0, 4.8)

Source: Adapted from Tables 1and 2, CDTL Memo
EOT - end of treatment visit, day 14-15; FV – final visit, day 28

In addition to the above primary and secondary analyses, Dr. Kadoorie conducted several sensitivity analyses, which showed that the results of the primary and secondary analysis were generally robust. Dr. Kadoorie also conducted exploratory analyses such as analyses of concordance/discordance with reasons for failures or indeterminate assessments at later visits in responders at 48-72 hours.

Overall, in Dr. Kadoorie's assessment, although the majority of comparisons tended to be slightly less favorable in the dalbavancin single-dose arm, treatment differences were still robust under the assumption of non-inferiority using a 10% NI margin. Dr. Kadoorie notes that there are still some limitations such as a few subgroups where primary and secondary analysis findings could potentially be less favorable to the dalbavancin single-dose arm (e.g. patients meeting systemic inflammatory response syndrome (SIRS) criteria or having fever at baseline),

Safety

In trial DUR001-303, 349 subjects received a single-dose regimen of dalbavancin and 346 subjects received the two-dose regimen. Four patients in the single-dose group received <1500 mg; three patients dalbavancin was discontinued prematurely due to an adverse event and one patient received a dose of 1000 mg due to an error in calculating the CrCl. The pooled safety database from all Phase 2/3 trials includes a total of 3697 patients, including 2473 patients treated with any dose of dalbavancin and 1224 patients treated with comparator.

There was one death in each treatment group. Neither death was considered related to study drug. The one death in the single-dose arm was due to intentional heroin and methamphetamine overdose and in the two-dose arm due to pulmonary embolism. Dr. Kapoor has reviewed the narratives and agrees with the investigator's assessment that the deaths were not related to study drug. Serious adverse events (SAEs) occurred in 7 (2.0%) and 5 (1.4%) patients in the single- and two-dose group, respectively. Dalbavancin was discontinued due to an adverse event in 6 (1.7%) patients in the single-dose group and in 5 (1.4%) patients in the two-dose group.

Treatment emergent adverse events (TEAEs) occurred in 70 (20.1%) and 69 (19.9%) patients in the single- and two-dose group, respectively. The most common TEAEs were nausea (3.4% and 2%), vomiting (1.7% vs 1.2%), headache (1.7% vs 0.9%), diarrhea (1.1% vs 0.6%) and dizziness (1.1% vs 0%) in the single and the two-dose group, respectively.

Hypersensitivity reactions occurred in 16 (4.6%) patients in the single-dose arm and in 13 (3.8%) patients in the two-dose arm. Infusion site reactions occurred in three patients in the single dose arm and in 7 patients in the two-dose arm. In the previously conducted dalbavancin trials, there was higher incidence of adverse events related to hemorrhages. Two cases were identified using a standardized MedDRA query (SMQ), one in each arm (vitreous hemorrhage in the single-dose arm and epistaxis in the two-dose arm). Both adverse events were mild, patients were on anticoagulants and were assessed by investigators as unrelated to study drug. Changes in laboratory test results or vital signs were similar between the treatment groups.

Hepatotoxicity

The potential for hepatotoxicity with dalbavancin is already described as a Warning in the package insert. Three patients in the single-dose group and two in the two-dose group had ALT elevations from normal baseline values to > 3 x the Upper Limit of Normal (ULN) post-dose. In the single-dose group, one patient each had post-dose ALT values of >5 x ULN to 10 x ULN, >10 x ULN to 20 x ULN, and >20 x ULN. In the two-dose group, one subject each had post-dose ALT values of >3 x ULN to 5 x ULN and >5 x ULN to 10 x ULN. All five patients had ALT elevations within first 15 days of drug exposure.

Post baseline ALT elevations of > 3 x ULN, irrespective of baseline values, occurred in total of 15 subjects (8 in single dose group and 7 in the two dose group). No patients met Hy's law criteria. However, one patient in the single-dose group with a history of hepatitis C, ongoing IV drug and alcohol abuse, with normal baseline and study day 4 liver tests, had ALT and AST >20 x ULN, total bilirubin >4 x ULN, and alkaline phosphatase > 2 x ULN at day 15. Liver tests abnormalities resolved by day 52. Concomitant medications included methadone.

Information in the package insert with respect to hepatotoxicity will be updated to reflect additional information obtained from Trial DUR001-303.

Analysis of pooled data from all (n=8) Phase 2 and 3 dalbavancin trials did not identify any new safety signals.

Since some glycopeptides are associated with prolongation of laboratory coagulation tests including activated partial thromboplastin time, prothrombin time and international normalized ratio (INR) due to interference with the test reagents, the Applicant was required to assess if there was interaction with coagulation tests as a postmarketing requirement. Results showed that dalbavancin at therapeutic levels did not artificially prolong prothrombin time (PT) or activated partial thromboplastin time (aPTT).

Drs. Kapoor and Kadoorie recommend approval of this sNDA. Dr. Iarikov, the CDTL also recommends approval of the sNDA. I agree with their assessment.

8.0 Labeling

Labeling recommendations from Jacqueline Sheppard, PharmD, from the Division of Medication Error Prevention and Analysis (DMEPA) provided for S-002 and Adam George, PharmD, from the Office of Prescription Drug Promotion (OPDP), have been incorporated in labeling. In her review dated November 11, 2015, for S-002, Dr. Sheppard found the Applicant's proposed carton and container labeling using the term single-use rather than single-dose to be acceptable.

9.0 Pediatrics

Pediatric trials for dalbavancin are currently underway. The Applicant had requested a deferral extension for PMR 2145-3: A Phase 3 pediatric safety and efficacy study of dalbavancin in the treatment of patients aged 3 months to < 18 years of age with ABSSSI. The deferral request was presented to the Pediatric Review Committee (PeRC) on December 02, 2015 and PeRC concurred with the Division's plan to grant the deferral extension. The proposed trial will evaluate both dosing regimens in children and hence no new pediatric studies are being required for the single-dose regimen.

10.0 Other Regulatory Issues

Clinical Site Inspections

John Lee, MD, from the Office of Scientific Investigations provided the clinical inspections summary for this sNDA. Three clinical sites were identified for GCP inspection, based on high subject enrollment and high efficacy rates at these sites. At these three sites (5% of 62, one foreign and two domestic), a total of 154 subjects (22% of 698) were enrolled. No significant deficiencies were observed at all three sites. A Form FDA 483 was issued only at Site 106, (b) (4) In Dr. Lee's assessment, the study conduct appeared adequate, including the Applicant's oversight of study conduct. The audited data were adequately verifiable and appear reliable as reported in the NDA. Dr. Lee notes that for all three sites, the Establishment Inspection Report (EIR) has not yet been received from the field office.

Advisory Committee Meeting

This sNDA was not discussed at an Advisory Committee meeting.

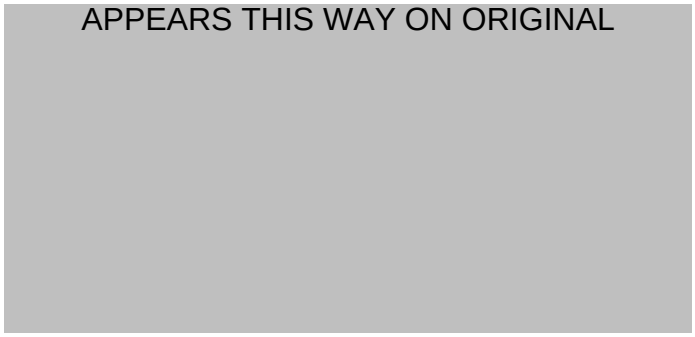
11.0 Risk Management

Safety information is adequately included in labeling. There are no new postmarketing commitments or requirements at this time based on this sNDA.

12.0 Recommended Regulatory Action

The Applicant has demonstrated the safety and efficacy of a single 1500 mg dose of dalbavancin administered intravenously in the treatment of adults with ABSSSI. The single adequate and well-controlled trial demonstrated that the single-dose regimen of 1500 mg was noninferior to the two-dose regimen of 1000 mg on day 1 followed by 500 mg a week later. No new safety signal was identified with the single-dose regimen. Labeling adequately describes the hepatotoxic potential of dalbavancin.

In summary, I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of a single 1500 mg dose of dalbavancin administered intravenously for the treatment of adults with ABSSSI. I recommend approval of this supplemental NDA (21883-/S-003).



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/s/

SUMATHI NAMBIAR
01/20/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dmitri Iarikov, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA # **Supplement#**	21-883 003
Applicant	Durata Therapeutics International, B.V.
Date of Submission	July 20, 2015
PDUFA Goal Date	January 20, 2016
Proprietary Name / Non-Proprietary Name	Dalvance™ (dalbavancin) for Injection
Dosage form(s) / Strength(s)	Lyophilized Powder for Injection / 500 mg
Applicant Proposed Indication/Population	Acute Bacterial Skin and Skin Structure Infections / Adults
Recommendation on Regulatory Action	Approval

1. Introduction

This supplemental NDA (sNDA) was submitted on July 20, 2015 to support a single-dose regimen of dalbavancin in the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. Dalbavancin is currently approved for the treatment of ABSSSI as a two-dose regimen with the doses administered one week apart.

The safety and efficacy of the single-dose regimen is supported by a Phase 3 double-blind, randomized non-inferiority trial in ABSSSI where a single dose of dalbavancin was compared with the approved two-dose regimen. The results of this trial are the main subject of this review.

2. Background

Dalbavancin is a lipoglycopeptide antibacterial drug that is approved for the treatment of ABSSSI caused by susceptible isolates of *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group.

Dalbavancin was approved on May 23, 2014 as a two-dose regimen of 1000 mg followed by 500 mg administered intravenously one week later. In patients with creatinine clearance (CrCl) less than 30 mL/min and not receiving hemodialysis, the dose is to be reduced to 750 mg followed by 375 mg one week later. The approval of the original NDA was supported by two Phase 3 randomized double-blind trials where dalbavancin was found to be non-inferior to

intravenous vancomycin with the option to switch to oral linezolid, studies DUR001-301 and -302.

This sNDA proposes an alternative single-dose dalbavancin regimen for the treatment of ABSSSI. The proposed dose is 1500 mg with dose reduction to (b) (4) mg in patients with renal impairment. The safety and efficacy of the regimen is supported by a Phase 3 trial comparing the single- and the approved two-dose regimen, study DUR001-303. The protocol of the trail was the subject of a special protocol agreement. The review of the supplement received a priority status.

3. CMC

The chemistry and manufacturing controls (CMC) review was conducted by Dr. Balajee Shanmugam. The product quality microbiology review was conducted by Daniel Schu. Both reviewers recommended approval of the sNDA.

Dalbavancin is synthesized from the natural glycopeptide A-40,926, a fermentation product of *Nonomuraea* sp. The final drug product consists of a single use vial with 500 mg dosage strength. The only CMC change associated with this efficacy supplement includes lowering a limit for endotoxins (from NMT 0.35 EU/mg to NMT 0.23 EU/mg) in the drug product specification. Otherwise, the CMC information remains unchanged from that of the approved NDA.

4. Nonclinical Pharmacology/Toxicology

No nonclinical studies were submitted with this sNDA. Dalbavancin nonclinical studies were reviewed at the time of the original NDA submission by Terry Miller, Ph.D and no additional studies were deemed necessary in relation to the single dose regimen.

Main dalbavancin toxicology findings included hepatocellular necrosis observed in dogs dosed at approximately 5 to 7 times the expected human dose on an exposure basis for longer than 2 months. Histiocytic vacuolation and hepatocyte necrosis were also observed in rats dosed daily for 4 weeks at approximately 3 times the expected human dose on an exposure basis. Microscopic changes were associated with ALT and AST elevation in both species. In addition, renal toxicity characterized by increases in serum BUN and creatinine and microscopic kidney findings were observed in rats and dogs at doses 5 to 7 times the expected human dose on an exposure basis. The relationship between these findings in the animals after more than 28 consecutive days of dosing to the single- or two-dose clinical dosing is uncertain.

Dalbavancin was not genotoxic. Impaired male and female fertility and increased embryo resorptions were observed in rats dosed at 3.5 times the expected human dose on an exposure basis.

5. Clinical Pharmacology

The clinical pharmacology reviewer for this sNDA as well as for the original dalbavancin NDA is Yang He, Ph.D. Clinical pharmacology studies submitted in this sNDA include an updated population PK analysis report, an animal PK/PD study in a neutropenic mouse model, and an *in vitro* study evaluating cytochrome P450 induction potential of dalbavancin in human hepatocytes.

A distinctive feature of dalbavancin is its long terminal half-life of 346 hours. Approximately 45% of a single dose of dalbavancin is excreted in urine through 42 days and 20% is excreted in feces through 70 days post dose. No dosage adjustment is necessary for patients with CrCl ≥ 30 mL/min or patients receiving hemodialysis. *In vitro* studies indicate that dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes. The antibacterial activity of dalbavancin appears to best correlate with the ratio of area under the concentration-time curve to minimal inhibitory concentration (AUC/MIC).

The updated population PK analysis report combined data from the new single dose Phase 3 trial and three clinical trials included in the previous population PK analysis. The estimated PK parameters of a single 1500 mg dose were overall comparable with those of two doses of 1000 mg on day 1 and 500 mg on day 8 except for a higher C_{max} associated with the single dose. In this analysis C_{max}, $AUC_{0\text{-}72hr}$, and $AUC_{0\text{-}14d}$ for the single and two-dose regimens were 411vs. 281mcg/mL•hr, 7350 vs. 5080 mcg/mL•hr, and 20300 vs. 18100 mcg/mL•hr, respectively.

The clinical pharmacology review is specifically focused on proposed dalbavancin dosing recommendation in patients with renal impairment and on susceptibility breakpoints.

Dosing recommendations in patients with renal impairment

In patients with severe renal impairment defined as CrCl < 30 mL/min, similarly to the approved two-dose regimen the single dose regimen is proposed to be adjusted. Based on the population PK modeling the applicant proposed to reduce the dose to (b) (4) from 1500 mg in these patients. The modeling predicted that the administration of (b) (4) of dalbavancin in patients with severe renal impairment will result in a 12% lower mean dalbavancin AUC at 15 days as compared to that predicted after the administration of 1500 mg of dalbavancin in patients with normal renal function.

The clinical pharmacology reviewer indicates that the proposed single (b) (4) dalbavancin dose for patients with CrCl < 30 mL/min appears to be acceptable because a 12% decrease in AUC is not considered to be meaningful based on a relatively large inter-patient variability of dalbavancin PK (i.e. clearance and AUCs). However, in order to align the total dosage of the single- and the approved two-dose regimen (750 mg and 375 mg one week later) for renally impaired patients, the reviewer recommends a single dose of 1125 mg (b) (4)
The reviewer also notes that a 1125 mg dose in patients with CrCl<30 mL/min would produce an AUC that would be nearly identical to that produced by a 1500 mg dose in patients with normal renal functions.

Susceptibility Interpretive Criteria

The current susceptible breakpoint for all bacterial species listed in the dalbavancin indications including *S. aureus* is ≤ 0.12 mcg/mL. The applicant proposes to increase the susceptible breakpoint to ≤ (b) (4) mcg/mL for all species. Dr. He recommends a susceptible breakpoint of ≤ 0.25 mcg/mL.

The new animal PK/PD study in the neutropenic mice evaluated dalbavancin AUC/MIC values associated with three target endpoints of net stasis, and 1- and 2-log reductions in *S. aureus* growth. In this study the three target endpoints were attained at AUC/MIC values that were several-fold lower than those observed in this model in the prior PK/PD study suggesting that higher susceptible breakpoints may be justified for dalbavancin. The difference in observed values of PK/PD targets in the new and prior study was attributed to the use of a more specific and accurate assay in the new study.

The target attainment analysis based on the new animal PK/PD study results showed that non-clinical PK/PD cutoff would support a susceptible breakpoint of (b) (4) Based on this information the applicant proposed to increase a susceptible breakpoint for all bacterial species listed in the dalbavancin indication from ≤ 0.12 mcg/mL to ≤ (b) (4) mcg/mL. No scientific rationale was provided, however, to support the selection of this particular breakpoint value.

Available surveillance and clinical data show that dalbvancin MIC_{90} values were ≤ 0.12 mcg/mL for all isolates of *S. aureus* including methicillin-resistant isolates*, S. pyogenes*, *S. agalactiae*, *S. dysgalactiae, Viridans Group Streptococci* and *E. faecalis*. In the two registrational Phase 3 dalbavancin trials the highest MIC value of 0.25 mcg/mL was reported for two isolates of *S. aureus* which upon retesting were found to have an MIC of 0.06 mcg/mL. There were no patients with MIC of ≥ 0.25 mcg/mL in the new trial.

Thus, the clinical pharmacology reviewer indicates that based on the available surveillance, nonclinical and clinical data, the proposed nonclinical PK/PD cutoff of (b) (4) mcg/mL may be excessive and its value in the determination of susceptibility breakpoints is limited because it may not be applicable to clinical setting. Of note, exposure-response analysis of patients from the new Phase 3 study evaluating the single-dose dalbavancin regimen concluded that there was no identifiable relationship between exposure and clinical response so exposure-response data were not used to support susceptibility breakpoints.

Based on the microbiological surveillance and clinical trial data, the clinical pharmacology reviewer concludes that a breakpoint of ≤ 0.25 mcg/mL rather than (b) (4) may be acceptable for all bacterial species listed in the dalbavancin indication. Additional microbiology information on dalbavancin is provided in the Clinical Microbiology section of this memorandum.

The clinical pharmacology review of this sNDA also included the study evaluating human cytochrome P450 induction potential of dalbavancin in human hepatocytes. The study results showed that dalbavancin at concentrations of up to 1000 µg/mL had no induction potential for CYP1A2.

6. Clinical Microbiology

The clinical pharmacology reviewer for this supplemental NDA is Kalavati Suvarna, Ph.D. For the review of the original NDA the reader is referred to the review by Dr. Peter Coderre dated February 20, 2014.

Dalbavancin is a glycopeptide antibacterial drug that binds to the D-alanyl-D-alanine portion of the nascent peptidoglycan pentapeptide and interferes with cell wall synthesis in gram-positive bacteria. Intrinsically glycopeptide-resistant species such as pediococci, leuconostoc, some species of lactobacilli, and bacteria expressing the *vanA* gene including vancomycin-resistant *S. aureus* (VRSA) are resistant to dalbavancin.

No new dalbavancin studies of mechanism of resistance, interaction with other antimicrobials, or bactericidal activity and time-to-kill were included in this sNDA. The new PK/PD study in neutropenic mice is described in section 5 Clinical Pharmacology of this memorandum. The discussion in this section will focus on the microbiological findings in the new study DUR001-303, dalbavancin MIC surveillance data, and breakpoint determination and complements the discussion on breakpoint determination provided in section 5 Clinical Pharmacology.

Microbiology findings in study DUR001-303
Baseline microbiological specimens collected in this study included lesion site culture and blood cultures. Microorganisms that were considered pathogens included *S. aureus, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus-milleri* group (*Streptococcus anginosus, Streptococcus intermedius, Streptococcus constellatus*), *Enterococcus faecalis, Enterococcus faecium,* and gram-positive anaerobes.

The microbiological intent-to-treat population (microITT) defined as all randomized patients who had at least one gram-positive pathogen isolated at baseline from either blood or ABSSSI lesion consisted of 430 subjects, including 210 and 220 subjects in the single- and two-dose group, respectively. The baseline MIC values for all pathogens ranged from 0.001 mcg/mL to 0.12 mcg/mL. The baseline MIC_{90} values for all pathogens were ≤ 0.06 mcg/mL. No post-baseline isolates with increase in dalbavancin MIC (≥4 fold increase in MIC value) were observed in this study. No correlation was observed between baseline dalbavancin MIC and clinical outcome in study DUR001-303.

Microbiology findings in pooled Phase 3 studies DUR001-301, -302, and -303
The baseline dalbavancin MIC values in these studies ranged from 0.001 mcg/mL to 0.25 mcg/mL. There were two *S. aureus* isolates (one methicillin-resistant and one methicillin susceptible) with MIC of 0.25 mcg/mL. The MIC values of these isolates retested at 0.06 mcg/mL. Dalbavancin MIC_{90} values for all isolates of all species were ≤ 0.06 mcg/mL.

Surveillance data
The microbiology reviewer analyzes surveillance data for the United States and European Union for 2002-2014 from the SENTRY surveillance study. There were more than 80,000 *S.*

aureus isolates with dalbavancin MIC ranging from ≤0.03 mcg/mL to 0.5 mcg/mL. Overall, a small fraction of *S. aureus* isolates had MIC of 0.25 mcg/mL and 0.5 mcg/mL. Thus, in 2011-2013 there were 40 out of 20,501 *S. aureus* isolates with MIC ≥ 0.25 mcg/mL, including 36 isolates with MIC of 0.25 mcg/mL and 4 isolates with MIC of 0.5 mcg/mL. Upon retesting MIC values of ≥ 0.25 mcg/mL were reproduced in 9 isolates including 4 isolates with MIC of 0.25 mcg/mL and 5 with MIC of > 0.25 mcg/mL. The dalbavancin MIC_{90} for *S. aureus* was ≤ 0.06 mcg/mL. The MIC distribution for methicillin-susceptible and resistant isolates was similar.

For *Streptococcus* spp. MIC values were ≤ 0.12 mcg/mL with the MIC_{90} of ≤ 0.06 mcg/mL. The dalbavancin MIC_{90} for *E. faecalis* ranged from 0.06 mcg/mL to 0.12 mcg/mL. Of note, for *E. faecalis* there was a small second population with MICs >0.25 mcg/mL which suggests a bimodal dalbavancin MIC distribution for *E. faecalis*. The number of isolates, however, in this second population was small.

Overall, clinical trial and surveillance data for *S. aureus* including methicillin-resistant isolates*, S. pyogenes*, *S. agalactiae*, *S. dysgalactiae, Viridans Group Streptococci* and *E. faecalis* showed similar MIC distributions with the dalbavancin MIC_{90} for all isolates of ≤ 0.12 mcg/mL.

Breakpoint determination

The current dalbavancin package insert include a susceptible breakpoint of ≤0.12 µg/mL for all pathogens included in the indication section, i.e. *S. aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*). The applicant proposed to increase the breakpoint to ≤ (b) (4) mcg/mL. In addition, the applicant proposed to add *Streptococcus dysgalactiae,* (b) (4) and *Enterococcus faecalis* to the dalbavancin indication and to the first list of microorganisms against which dalbavancin is active in the Microbiology section of the package insert.

The microbiology reviewer notices that there are no clinical data to support the breakpoint of (b) (4) mcg/mL. The reviewer indicates that dalbavancin clinical studies and surveillance data support a susceptible breakpoint of 0.12 mcg/mL for *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible strains) whereas PK/PD target attainment analyses support a susceptible breakpoint of 0.25 mcg/mL. In conclusion, the microbiology reviewer recommends a susceptible breakpoint of 0.25 mcg/mL for all these species.

Regarding the inclusion of additional pathogens to the dalbavancin package insert, the microbiology reviewer notices that (b) (4) should not be included as it is not considered a pathogen for ABSSSI whereas *Streptococcus dysgalactiae* and *Enterococcus faecalis* (vancomycin-susceptible stains) may be included.

7. Clinical/Statistical - Efficacy

The clinical review was conducted by Rama Kapoor, M.D, and the statistical review was conducted by Christopher Kadoorie, Ph.D. The reviewers conclude that adequate evidence of efficacy of a single dose of dalbavancin in the treatment of ABSSSI have been provided and are in agreement regarding interpretation of the trial results.

The efficacy of a single-dose regimen of dalbavancin for the treatment of ABSSSI was supported by a Phase 3 trial comparing a single dose of dalbavancin with the approved two-dose regimen, study DUR001-303. This was a randomized, double-blind, non-inferiority trial. Patients in the single-dose group received dalbavancin 1500 mg on day 1 followed by placebo on day 8. Patients in the two-dose group received dalbavancin 1000 mg on day 1 followed by dalbavancin 500 mg on day 2. In patients with CrCl < 30 mL/min and not receiving hemodialysis the dalbavancin dose was reduced to 1000 mg in the single- and to 750 mg on day 1 followed by 375 mg on day 8 in the two-dose group.

The enrollment criteria in the trial were consistent with those recommended by the latest FDA guidance on developing drugs for treatment of ABSSSI[1]. Enrollment of patients with major abscesses was capped at 30%.

The primary efficacy endpoint was clinical response at 48 to 72 hours after the initiation of study drug in the intent-to-treat (ITT) population. The clinical response was defined as a decrease of ≥ 20% in lesion area provided that the patient is alive and has received no rescue therapy for ABSSSI. Patients who had missing lesion measurements at baseline or in the 48-72 hours after the initiation of study drug were classified as non-responders. The ITT population included all randomized patients regardless of whether or not they received study drug. A 10% non-inferiority margin was used to determine treatment efficacy in the primary analysis.

Key secondary efficacy endpoints included clinical success at the end of treatment (day 14-15) and final (day 28) visits. Of note, sustainability of dalbavancin treatment effect was the focus of special attention during special protocol agreement discussion because in one of the registrational dalbavancin trials a lower clinical success rate at day 26 to 30 was observed in the dalbavancin arm. Thus, for trial DUR001-003 the Division pre-specified criteria with respects to efficacy comparisons at the final visit (day 28). The requirement stipulated that the lower limit of the 95% CI for the difference in clinical success at the final visit in the ITT population must be no less than -15% in order for the trial to be considered successful.

Clinical success at the final visit was defined as a decrease in lesion area by ≥ 90% from baseline, the patient's temperature ≤ 37.6°C, tenderness to palpation and swelling no worse than mild and absent fluctuance and warmth. Clinical success at the end of treatment (EOT) visit was defined as a decrease in lesion area by ≥ 80 % from baseline, the patient's temperature ≤ 37.6°C, and all local signs of infection no worse than mild.

[1] Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment, October 2013. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071185.pdf

A total of 698 subjects were randomized and 349 subjects were included in each treatment group. Demographic and baseline characteristics were similar between the two treatment groups. The mean age was 48 years. Approximately 58% of subjects were males. The majority of patients were White (~89%). Approximately 45% were enrolled in the United States. The most common infection type was cellulitis (~47%) followed by wound infection (~26%) and major abscess (~26%).

The median lesion area of cellulitis was 376 cm^2 and 345 cm^2 in the single- and two-dose group, respectively. The most commonly isolated pathogen in both groups was *S. aureus* (~65.5%); methicillin-resistant isolates constituted 17% and 24.5% in the single- and two-dose group, respectively.

In this trial a single-dose regimen of dalbavancin met the pre-specified criteria for non-inferiority to the two-dose regimen. The results of the primary analysis are shown in **Table 1**.

Table 1: Primary Efficacy Analysis: Clinical Response at 48-72 hours (ITT population)		
Dalbavancin Dose Group		
Single-Dose n/N (%)	**Two-Dose n/N (%)**	**Treatment difference (95% CI)**
284/349 (81.4)	294/349 (84.2)	-2.9 (-8.5, 2.8)
Source: Adapted from table 5, Statistical Reviewer review		

There was also no difference in the rate of clinical success between study groups at the secondary endpoints. The statistical reviewer primary and key secondary analyses were identical to those of the applicant.

Table 2: Secondary Efficacy Analysis: Clinical Success Rates at End-of-Treatment and Final Visits (ITT population)			
	Dalbavancin Dose Group		
	Single-Dose n/N (%)	**Two-Dose n/N (%)**	**Treatment difference (95% CI)**
Clinical Success at EOT	293/349 (84.0)	296/349 (84.8)	-0.9 (-6.3, 4.6)
Clinical Success at FV	295/349 (84.5)	297/349 (85.1)	-0.6 (-6.0, 4.8)
EOT - end of treatment visit, day 14-15; FV – final visit, day 28 Source: Adapted from table 6, Statistical Reviewer review			

I agree with Dr. Kapoor and Dr. Kadoorie conclusions that provided efficacy data are adequate to support approval of a single dose dalbavancin regimen for the treatment of ABSSSI. The pivotal Phase 3 trial included in this submission met its primary objective by demonstrating that the single-dose regimen is non-inferior to the approved two-dose regimen. Similar clinical response in both treatment groups at day 28 satisfied the additional requirement from the Division to ensure the sustainability of treatment effect.

8. Safety

The clinical review was conducted by Dr. Rama Kapoor. She concludes that the safety profile of the single 1500 mg dose regimen of dalbavancin in the treatment of ABSSSI is acceptable and recommended approval of this sNDA.

A total of 695 subjects received dalbavancin in trial DUR001-303 including 349 subjects in the single- and 346 subjects in the two-dose group. There were 2 subjects (0.6%) in the single-dose and 7 subjects (2.0%) in the two-dose group who had CrCl <30 mL/min, were not on dialysis and received reduced doses of dalbavancin.

There was 1 patient in each treatment group who died during the study. Neither death was considered related to study drug. Serious adverse events occurred in 7 (2.0%) and 5 (1.4%) subjects in the single- and two-dose group, respectively. Dalbavancin was discontinued due to an adverse event in 6 (1.7%) subjects in the single-dose group and in 5 (1.4%) subjects in the two-dose group.

Any treatment emergent adverse events (TEAEs) occurred in 70 (20.1%) and 69 (19.9%) subjects in the single- and two-dose group, respectively. There were no noticeable differences between the treatment groups in the incidence and duration of TEAEs including infusion site or hypersensitivity reactions. There were also no noticeable differences in laboratory findings or vital signs changes between the treatment groups.

Alanine aminotransferase (ALT) elevations were the subject of special attention during safety evaluation. Safety analyses of the initial dalbavancin NDA demonstrated that a higher percentage of dalbavancin- than comparator-treated patients had on treatment ALT elevations. These findings resulted in a warning in the dalbavancin package insert stating that in Phase 2 and 3 clinical trials more dalbavancin- than comparator-treated subjects with normal baseline transaminase levels had post-baseline ALT elevation greater than 3 times the upper limit of normal.

In trial DUR001-303 there were 5 subjects with ALT risen from normal baseline values to > 3 x ULN post-dose including 3 subjects in the single-dose group and 2 subjects in the two-dose group, **Table 3**. The ranges of post dose ALT elevation for 3 subjects in the single-dose group were >5x ULN - 10x ULN, >10x ULN - 20x ULN, and >20x ULN with one subject in each range. For 2 subjects in the two-dose group the ranges of post baseline ALT elevation were >3x ULN -5x ULN and >5x ULN - 10x ULN with one subject in each range. No significant post baseline shifts in liver tests were observed in subjects with abnormal baseline liver tests.

Table 3: Post-Baseline ALT Shift in Trial DUR001-303				
Post-Baseline ALT	**Baseline ALT**			
Single-Dose Group	≤ ULN n=302	> ULN – 3x ULN n=43	>3x ULN - 5x ULN n=0	>5x ULN - 10x ULN n=0
≤ ULN	262	5	0	0
ALT > ULN - 3x ULN	37	33	0	0
ALT > 3xULN - 5x ULN	0	5	0	0
ALT > 5xULN -10x ULN	1	0	0	0
ALT >10xULN - 20x ULN	1	0	0	0
ALT >20x ULN	1	0	0	0
Two-Dose Group	≤ ULN n=291	> ULN – 3x ULN n=45	>3x ULN - 5x ULN n=5	>5x ULN - 10x ULN n=1
≤ULN	252	7	0	0
ALT > ULN - 3x ULN	37	36	3	0
ALT > 3x ULN - 5x ULN	1	1	2	1
ALT > 5x ULN - 10x ULN	1	1	0	0
ALT >10x ULN - 20x ULN	0	0	0	0
ALT >20x ULN	0	0	0	0
Source: Adapted from Table 43, Medical Officer review				

No patients met Hy's law criteria. However, one patient in the single-dose group while not formally meeting Hy's law criteria due to a history of liver disease developed liver tests abnormalities otherwise consistent with Hy's law criteria. This 57-year-old male with lower leg cellulitis, a history of hepatitis C, ongoing IV drug and alcohol abuse but with normal baseline and study day 4 liver tests, at day 15 was found to have ALT and AST >20 x ULN, total bilirubin >4 x ULN, and alkaline phosphatase > 2 x ULN. Liver tests abnormalities resolved by day 52.Concomitant medications included methadone

The absence of a non-dalbavancin comparator makes the safety analyses of trial DUR001-003 somewhat limited. However, the findings in this trial confirm prior observations that dalbavancin may be associated with a high degree of ALT elevation. While the highest levels of post-dose ALT elevations in this trial were observed in the single-dose group, given a small number of subjects with post-dose ALT > 3x ULN no definitive conclusions can be made.

The submission also included pooled data from all (n=8) Phase 2and 3 dalbavancin trials which included 2473 subjects treated with any dose of dalbavancin and 1224 subjects treated with comparators. The analysis of these data does not suggest any new dalbavancin-associated safety signals.

I agree with Dr. Kapoor conclusions that the results of trial DUR001-303 demonstrate an acceptable safety profile of a single 1500 mg dose regimen of dalbavancin in the treatment of ABSSSI.

9. Advisory Committee Meeting

No advisory committee meeting was convened for this supplemental NDA.

10. Pediatrics

The applicant submitted a pediatric plan to study a single-dose dalbavancin regimen in treatment of ABSSSI in patients 0-18 years of age and requested a deferral of pediatric studies. The pediatric plan for this sNDA includes two Phase 3 studies in children with ABSSSI, one study in children from 3 months to 17 years and another in children from birth to 3 months. The studies will include a single- and two-dose dalbavancin treatment groups in addition to a comparator group. The pediatric plan was discussed at the Pediatric review Committee (PeRC) and found to be acceptable. The proposed pediatric studies will be postmarketing requirements.

11. Other Relevant Regulatory Issues

A clinical inspection summary (CIS) report was completed by John Lee, M.D. on December 11, 2015. Three out of 62 clinical sites were selected for inspection for large contribution to the overall study outcome. The selected sites were the three largest sites with a higher responder rates as compared to the other sites, 95% vs. 79%, respectively.

No significant deficiencies were observed at all three sites. The study conduct appeared adequate, including the sponsor's oversight of study conduct. All audited data were adequately verifiable and appear reliable as reported in the NDA. Of note, at the time this review is written, the establishment inspection report has not been received from the field office and the final inspection outcome remains pending.

12. Labeling

The selection of an appropriate term for carton and container labeling, specifically the term "single-use" or "single-dose" vial, was the subject of discussion during the review. The Division is aware that a draft FDA guidance on selection of terms for labeling recommends the term "single-dose" to label vials designed for use in a single patient as a single infusion. The Division is concerned, however, that with the approval of the single-dose dalbavancin regimen the use of the term "single-dose" for dalbavancin vials may result in dosing errors. Dalbavancin is distributed in 500 mg vials and the proposed 1500 mg single-dose regimen (or 1125 mg in patients with renal impairment) requires three vials. Labeling of a vial as a "single-dose" may imply that one vial constitutes the full single-dose regimen and result in administering of a sub-therapeutic dose.

Notably, similar concerns regarding a potential for medications errors related to the use of the term "single-dose" in container labeling have been expressed in comments submitted to the draft guidance docket, as well as in communications sent by the applicant to the Division.

Considering unique aspects of dalbavancin dosing, the Division decided to use the term "single-use" rather than "single-dose" in the labeling of the carton and container. The Division discussed its decision with the Division of Medication Error Prevention and Analysis and the Office of Product Quality. The Division will await the final version of the draft FDA guidance on package type terms to inform its further decisions on container labeling.

Other pertinent labeling recommendations included updates in the list of pathogens in the dalbavancin indication and in the first list of microorganisms against which dalbavancin is active and updates in dalbavancin breakpoints. These recommendations are discussed in the Clinical Pharmacology and Clinical Microbiology section of this memorandum.

(b) (4)

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend approval of the sNDA for a single-dose regimen of dalbavancin in the treatment of adults with acute bacterial skin and skin structure infections. I agree with the primary reviewers that the applicant has provided sufficient evidence to support the safety and efficacy of the regimen. Dalbavancin was non-inferior to the approved two-dose dalbavancin regimen in an adequate and well-controlled Phase 3 trial. No specific safety concerns related to the single-dose dalbavancin regimen have been identified.

Recommendations for Postmarketing Requirements

The postmarketing requirements include two pediatric studies. These studies are also part of the postmarketing requirements for the original NDA. The studies will include a single-dose group in addition to a two-dose and comparator groups. The postmarketing requirements and agreed upon timelines are as follows:

1. Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from 3 months to 17 years of age with ABSSSI.

   Study Completion: June 2017
   Final Report Submission: December 2017

2. Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in neonates/infants from birth to less than 3 months of age with ABSSSI.

   Final Protocol Submission: December 2016
   Study Completion: December 2019
   Final Report Submission: June 2020

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

/s/

DMITRI IARIKOV
01/19/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b) (1) New Drug Application
Application Number	21883
Priority or Standard	Priority
Submit Date	07/20/2015
Received Date	07/20/2015
PDUFA Goal Date	01/20/2016
Division / Office	Division of Anti-Infective Products / Office of Antimicrobial Products
Reviewer Name	Rama Kapoor, MD
Review Completion Date	November 27, 2015
Established Name	Dalbavancin hydrochloride (HCl)
Trade Name	DALVANCE
Therapeutic Class	Lipoglycopeptide antibacterial
Applicant	Durata Therapeutics International B.V.
Formulation	Sterile, lyophilized powder; Intravenous
Dosing Regimen	1500 mg, administered either as a single dose, or 1000 mg followed one week later by 500 mg. For patients with creatinine clearance < 30 mL/min and not on hemodialysis: 1000 mg, as a single dose, or 750 mg followed one week later by 375 mg. No dosage adjustment is recommended for patients receiving regularly scheduled hemodialysis
Indication	Acute bacterial skin and skin structure infections (ABSSSI)
Intended Population	Adult

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Dalbavancin 1500 mg as an intravenous (IV) single dose regimen should be approved for the treatment of acute bacterial skin and skin structure infection (ABSSSI) caused by susceptible organisms in adults.

Efficacy and safety data from trial DUR001-303 comparing dalbavancin single dose of 1500 mg with the already approved dalbavancin two dose regimen (1000 mg on day 1, followed by 500 mg on day (b) (4), and a supportive integrated safety data from all dalbavancin phase2/3 studies, provide an adequate evidence to recommend the approval of a dalbavancin single dose regimen of 1500 mg as a safe and efficacious treatment for ABSSSI caused by susceptible organisms in adults.

No deficiencies were identified in this supplemental NDA that would preclude the approval.

1.2 Risk Benefit Assessment

The overall risk benefit profile of the dalbavancin 1500 mg single dose regimen in the treatment of ABSSSI is favorable. Dalbavancin 1500 mg single dose regimen demonstrated similar efficacy as its comparator dalbavancin two dose regimen (1000mg on day 1 followed by 500 mg on day 8) using both primary end point and secondary endpoints in a Phase 3b, randomized, double blind, multicenter trial DUR001-303. The trial met the primary objective of demonstrating non-inferiority of dalbavancin single dose to a two dose regimen based on early clinical response at 48-72 hours using a 10% non-inferiority margin.

Additional potential benefits of the single dose regimen are that the drug can be given only once which is favorable in terms of patient compliance and that there is no need for an oral step-down therapy. Dosing adjustment is not needed except for patients with creatinine clearance is less than 30 mL/min, who are not on hemodialysis or peritoneal dialysis, where a dosing guideline has been provided by the Applicant.

The primary efficacy endpoint in this trial was clinical response at 48 to 72 hours (± 3 hours) post-study drug initiation in the ITT population defined by patient being alive and having received no rescue therapy and with a decrease of ≥20% in lesion area relative to the baseline measurement. The responder rate in trial DUR001-303 was 81.4% in the dalbavancin single dose group as compared to 84.2% in the two dose group resulting in a treatment difference of -2.9 (95% confidence interval (CI): [-8.5 to 2.8]). The lower level of the 95% CI for the treatment difference in the ITT population exceeded the pre-specified lower limit of -10% in this study.

The trial also satisfied the secondary end points. The clinical status in the clinically evaluable (CE) population and intent to treat (ITT) population at the end of treatment (EOT) visit and clinical status in the CE population and ITT population at the Final Visit, were analyzed as secondary efficacy endpoints. The proportions of patients in the ITT and CE populations who demonstrated clinical success at EOT were similar across treatment groups, as were the proportions of patients who demonstrated clinical success at the Final Visit. Of note, clinical success at the EOT visit was defined differently than clinical success at the Final Visit. For evaluation at the EOT visit, the patient's lesion area must be decreased by ≥80% from baseline, and for evaluation at the Final Visit, the patient's lesion area must be decreased by ≥90% from baseline. The success rate in clinical status at EOT and Final Visit in ITT population were 84.0% vs 84.8%, 95% CI -0.9 (-6.3 to 4.6) and 84.5% vs 85.1%, 95% CI -0.6 (-6.0 to 4.8) in the single dose and two dose groups respectively. Similarly, for success rates in clinical status at EOT and Final Visit in CE population, comparisons were 88.4% vs. 89.4%, 95% CI -1.0 (-6.1 to 4.1) and 92.3% vs. 92.5%, 95% CI -0.3 (-4.9 to 4.4) in the single dose and two dose groups respectively.

The Applicant demonstrated an acceptable safety profile for the dalbavancin single dose regimen with similar fatal and non-fatal adverse events as for the two dose regimen. The incidences of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) were low in this trial and similar between the study groups.

The significant safety finding was liver transaminase elevations indicating the possibility of dalbavancin-associated hepatocellular liver injury, especially in subjects with underlying liver disease. Higher rates of ALT elevation greater than 3 times the upper limit of normal in subjects with normal baseline ALT were also noted in dalbavancin-treated subjects in prior dalbavancin trials and lead to a warning in the dalbavancin package insert. Transaminase elevations occurred within day 3 to 35 of dalbavancin administration implying their temporal relationship to dalbavancin exposure. Most patients returned to within the normal range subsequently without intervention. None of these transaminase elevations was associated with a fatal outcome or met Hy's law criteria. Neither post marketing reports from the Applicant, nor have published cases of liver failure associated with the drug been reported.

The Applicant also performed an analysis of ALT elevations on day 3 to evaluate whether an increased exposure to dalbavancin concentrations (both AUC and Cmax) in the single-dose as compared to the two-dose treatment regimen had an effect on ALT elevations post-baseline. The frequency of post-baseline ALT elevations on day 3 in the single-dose group was marginally lower than that observed in the two-dose group. However, ALT elevations were frequently observed at day 14 in dalbavancin trials, hence the sensitivity of this analysis at day 3 in terms of correlation of dalbavancin exposure and ALT elevations may be limited.

Based on these observations, this reviewer recommends that the warning on ALT elevation associated with dalbavancin use remain in the Warnings and Precautions section of dalbavancin package insert.

In summary, the Applicant has submitted adequate data demonstrating an acceptable efficacy and safety profile of a single 1500 mg dose regimen of dalbavancin in the treatment of ABSSSI to recommend its approval.

1.3 Recommendations for Post market Risk Evaluation and Mitigation Strategies

Post marketing risk management activity must include post marketing reporting of adverse drug experiences as outlined in 21 CFR 314.80. This reviewer recommends that the incidence of liver transaminase elevations and drug induced liver injury be monitored as part of routine pharmacovigilance for this product.

1.4 Recommendations for Post market Requirements (PMRs) and Commitments

A total of six PMRs including four pediatric studies were requested at the time of approval of original NDA 21883. No additional postmarket requirements or commitments are expected upon approval of this efficacy supplement provided that the supplement is approved. The current status of dalbavancin PMRs is cited below:

PMR 2145-1: Phase 1 PK study in children aged 3 months to < 12 years. The study was initiated in 2013. A final report is expected by March 2016.

PMR 2145-2: Phase 1 PK study in children aged 0 to < 3 months. The study is projected to be completed in May 2017 with final report submission in November 2017.

PMR 2145-3: Phase 3 randomized comparator-controlled study of dalbavancin in children from 3 months to 17years of age with ABSSSI. The protocol for this study was revised to include a single-dose treatment arm, based on a recommendation from the Division. The Applicant submitted a deferral request for study completion and report submission. The request is justified by the need to assess safety and efficacy of a single-dose dalbavancin regimen in adults before initiating the study in children. The Division agreed to grant the deferral. According to the revised timeline the study is expected to be competed in June 2017 and final report will be submitted in December 2017.

PMR 2145-4: Phase 3 randomized comparator-controlled study in children 0 to < 3 months of age with ABSSSI. Target date for study completion is December 2019 and for and final report submission is June 2020.

In addition to the pediatric studies, the Applicant was required to conduct the following PMRs:

2145-5: Conduct US surveillance studies for five years from the date of marketing DALVANCE to determine if resistance to dalbavancin has developed in those organisms specific to the indication in the label of ABSSSI. The study is projected to be completed in September 2019 with final report submission in September 2020.

2145-6: Conduct studies to define the mechanism(s) of resistance for isolates identified as being resistant to dalbavancin during the surveillance period (five years from the date of marketing). The study is projected to be completed in September 2019 with final report submission in September 2020.

2 Introduction and Regulatory Background

2.1 Product Information

Dalbavancin is a second generation semi-synthetic lipoglycopeptide antibacterial drug. Its mechanism of action involves the interruption of cell wall synthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits. This disruption of the cell wall results in bacterial cell death. Dalbavancin was approved by FDA on May 23, 2014 for the treatment of adult patients with ABSSSI caused by susceptible strains of the following gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-resistant [MRSA] strains)
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S.*
- *constellatus*)

Dalbavancin is synthesized from a fermentation product of *Nonomuraea sp*. Dalbavancin drug substance is a hydrochloride salt and is a mixture of 5 closely related homologs. The homologs differ from one another in the length and/or branching of their respective fatty acid side chains on the N-acylaminoglucuronic acid moiety and/or the presence of an additional methyl group on the N-terminus of the peptide. The major homolog (> 80%) is designated B0. The B0 chemical name is: 5, 31-dichloro-38-de (methoxycarbonyl)-7-demethyl-19-deoxy- 56-*O*-[2-deoxy-2-[(10-methyl-1-oxoundecyl) amino]-β-D-glucopyranuronosyl]-38- [[[3-(dimethyl amino) propyl] amino] carbonyl]-42-*O*-β-D-mannopyranosyl- *N*15-methylristomycin An aglycone hydrochloride. (**Figure 1**)

Dalbavancin hydrochloride salt is freely soluble in water. It is administered IV over a 30-minute period. Because of its long elimination half-life the proposed clinical dosage

regimen in patients with creatinine clearance ≥ 30 mL/min or who are receiving regularly scheduled renal dialysis consists of 1500 mg, administered either as a 1000-mg dose on day 1 followed by a 500-mg dose on day 8, or a single dose of 1500 mg. Patients with creatinine clearance (CrCl) of less than 30 mL/min and not receiving dialysis should receive either a 2-dose regimen of 750 mg dose on day 1 and a 375 mg dose on day 8, or a single dose of (b) (4)

A dose adjustment is not required for subjects with hepatic impairment.

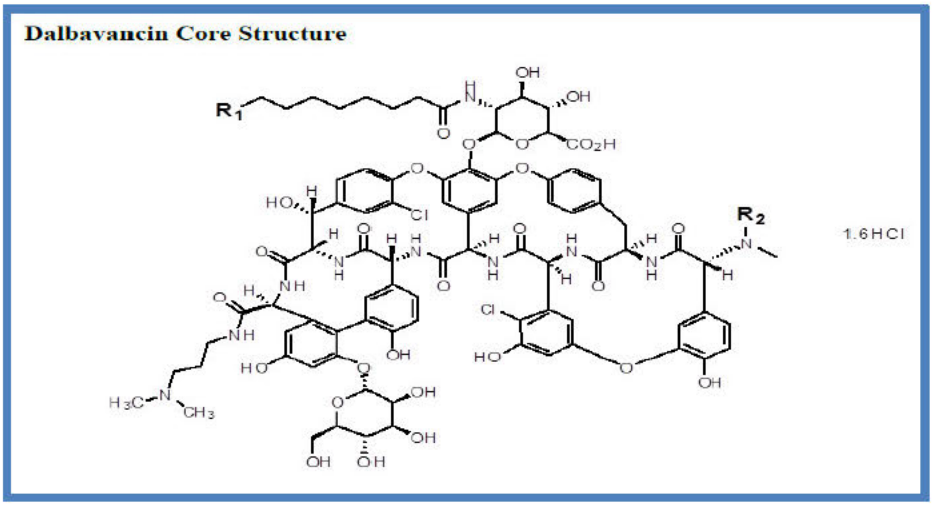

Figure 1 General Structure of Dalbavancin API

2.2 Tables of Currently Available Treatments for Proposed Indications

Products currently available for the treatment of skin and skin structure infections are presented in **Table 1**. Antibacterial drugs with the following indications are included: skin and skin structure infections, skin and soft tissue infections (SSTI), serious skin and soft tissue infections, complicated skin and skin structure infections (cSSSI), and acute bacterial skin and skin structure infection (ABSSSI). Products labeled for the treatment of uncomplicated skin and skin-structure infections are not included.

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

Product Generic Name*	Routes
AMOXICILLIN AND CLAVULANATE	Oral
AMIKACIN SULFATE	Intramuscular and Intravenous
AMPICILLIN, SULBACTAM	Intramuscular and Intravenous

AZTREONAM	Intravenous
CEFACLOR	Oral
CEFADROXIL HEMIDRATE	Oral
CEFAZOLIN SODIUM	Intravenous
CEFOTAXIME	Intramuscular and Intravenous
CEFOTETAN	Intravenous
CEFOXITIN	Intravenous
CEFTAROLINE FOSAMIL	Intravenous
CEFTAZIDIME	Intravenous
CEFTRIAXONE	Intramuscular and Intravenous
CEPHALEXIN	Oral
CIPROFLOXACIN	Intravenous and Oral
CLINDAMYCIN	Intravenous and Oral
DAPTOMYCIN	Intravenous
DEMECLOCYCLINE HYDROCHLORIDE	Oral
ERYTHROMYCIN	Oral
ERTAPENEM SODIUM	Intramuscular and Intravenous
GENTAMICIN	Intramuscular and Intravenous
IMIPENEM AND CILASTATIN SODIUM	Intravenous
LEVOFLOXACIN	Intravenous and Oral
LINEZOLID	Intravenous and Oral
MEROPENEM	Intravenous
METRONIDAZOLE	Intravenous and Oral
MINOCYCLINE	Intravenous and Oral
MOXIFLOXACIN HYDROCHLORIDE	Intravenous and Oral
ORITAVANCIN	Intravenous
PIPERACILLIN SODIUM,TAZOBACTAM	Intravenous
QUINUPRISTIN AND DALFOPRISTIN	Intravenous
TELAVANCIN HYDROCHLORIDE	Intravenous
TETRACYCLINE HYDROCHLORIDE	Oral
TEDIZOLID PHOSPHATE	Intravenous and Oral
TIGECYCLINE	Intravenous
TOBRAMYCIN SULFATE	Intravenous
VANCOMYCIN HYDROCHLORIDE	Intravenous

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

- Daptomycin
- Linezolid
- Oritavancin
- Tigecycline
- Vancomycin
- Ceftaroline

- Tedizolid

Medications approved for "serious skin and soft tissue infections" are cefazolin, clindamycin, and tetracycline.

2.3 Availability of Proposed Active Ingredient in the United States

Dalbavancin is approved in the United States as a two dose regimen for the treatment of adult patients with ABSSSI caused by susceptible strains of gram positive organisms.

2.4 Important Safety Issues with Consideration to Related Drugs

Dalbavancin is structurally related to other glycopeptides like vancomycin, telavancin and oritavancin and may exhibit a similar adverse reaction profile. The adverse reactions associated with these drugs include infusion related events including phlebitis, flushing of the upper body during rapid infusion, nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia.

Of note, as compared to some other lipoglycopeptides such as telavancin and oritavancin, dalbavancin does not artificially prolong prothrombin time or activated partial thromboplastin time. The absence of dalbavancin interference with coagulation tests was assessed in an *in vitro* study and this information is included in the dalbavancin package insert.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clinical trials of dalbavancin have been undertaken since 1999. Prior to acquisition of dalbavancin by Durata Therapeutics, Inc. (hereafter Durata) in December 2009, four other sponsors had developed dalbavancin under the names of VER001, PF-03906135, BI-397 and V-Glycopeptide. NDA 21-883 was initially submitted to FDA in December 2004 for the indication of complicated skin and skin structure infections (cSSSI) by Vicuron Pharmaceuticals Inc., a subsidiary of Pfizer. The application was supported by a phase 3 trial in cSSSI (VER001-9). In this trial dalbavancin met the pre-specified criteria for non-inferiority to linezolid in the co-primary efficacy analyses of clinical response at the test-of-cure (TOC) visit in the Intent-to-Treat (ITT) and in the Clinically Evaluable (CE) populations. The application also included a supportive study of uncomplicated skin and skin structure infections (uSSSI) requiring parenteral therapy (VER001-8). Pfizer, however subsequently withdrew NDA 21-883 (b) (4) .

Durata assumed the sponsorship of dalbavancin in December 2009 and in January

2011, initiated a clinical development program that included two new randomized phase 3 trials for the treatment of ABSSSI. On September 26, 2013, Durata resubmitted NDA 21-883. Dalbavancin demonstrated non-inferior efficacy for the two-dose dalbavancin regimen relative to a comparator regimen of twice-daily vancomycin IV with an option to switch to oral linezolid after 3 days. Based on the results of these two trials, dalbavancin was approved in the United States on May 23, 2014 for the treatment of adult patients with ABSSSI. The approved dosage is a two-dose regimen of 1000 mg followed one week later by 500 mg, each administered over 30 minutes via IV infusion (with dosage adjustment to 750 mg followed one week later by 375 mg in patients with creatinine clearance rate (CrCl) <30 mL/min who do not receive regularly scheduled hemodialysis).

Subsequently, on March 24, 2014, the Sponsor reached a Special Protocol Agreement (SPA) with FDA regarding Protocol DUR001-303 a Phase 3b, multicenter, double-blind clinical trial to compare the efficacy and safety of a single 1500 mg dose of dalbavancin with dosage adjustment to 1000 mg in patients with CrCl<30 mL/min who are not receiving hemodialysis to the approved two-dose dalbavancin regimen in treatment of adult patients with ABSSSI. The results of this new trial are the main subject of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This clinical reviewer performed a review of random sample of 10% of the case report forms (CRFs) from DUR001-303 ABSSSI trial to verify the accuracy of the transcription of data from the CRFs to the datasets and to check for agreement with the Applicant's evaluability and outcome determinations. The quality and integrity of the submission are acceptable. The submission uses the electronic common technical document (eCTD) format. The submission is well organized and easy to navigate. Submitted Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets meet the Clinical Data Interchange Standards Consortium (CDISC) standards.

3.2 Compliance with Good Clinical Practices

For the studies included in this sNDA, the Applicant stated that institutional review board approval was obtained for each center, that the studies were conducted according to ethical principles originating in the Declaration of Helsinki and consistent with International Conference on Harmonization (ICH) good clinical practice guidance, and that informed consent was obtained from all subjects before the start of any study procedures.

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) stating that it had not entered into any financial arrangement with the listed clinical investigators in which compensation to the investigator could be affected by the outcome of the study. The Applicant also reported that there were no disclosable financial interests for any of the responding principal or site investigators. Please see eCTD 1078, module 1.3.4 for Financial Disclosure Review.

Medical reviewer's Comment: This reviewer considers the disclosures to be acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

Dalbavancin is synthesized from a fermentation product of *Nonomuraea sp*. The drug substance, dalbavancin hydrochloride, is a semi-synthetic purified lipoglycopeptide. Dalbavancin hydrochloride is a mixture Dalbavancin is a mixture of five active homologs (A0, A1, B0, B1, and B2) with B0 being the major component of dalbavancin comprising >80% of the drug product. The homologues share the same core structure and differ in the fatty acid side chain of the N-acylaminoglucuronic acid moiety (R1) structure and/or the presence of an additional methyl group (R2) on the terminal amino group. The drug product is manufactured (b) (4) The chemistry reviewer concluded that the NDA has provided sufficient information to assure identity, strength, quality, purity, potency and bioavailability of dalbavancin and the finished drug product, dalbavancin for injection. Reader is referred to the review by CMC reviewer for additional details.

4.2 Clinical Microbiology

Dalbavancin has shown activity against gram-positive bacteria associated with ABSSSI including *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group (including *S. anginosus, S. intermedius, and S. constellatus*) and *Enterococcus faecalis*. Dalbavancin is not active against VanA expressing Enterococcus species. The dalbavancin MIC90 against vancomycin resistant *Enterococcus species* (VRE) is >0.25 µg/mL in the US and Europe.

4.2.1 Determination of Breakpoints or Susceptibility interpretive criteria

(b) (4)

The Applicant proposes to change the breakpoints for dalbavancin from 0.12 µg /mL to µg /mL for *Staphylococcus aureus* and other gram positive bacteria listed above. The breakpoints are proposed based on the surveillance data, PK-PD studies in the neutropenic mouse thigh infection model, human PK data, and susceptibility of baseline isolates and outcomes in the clinical trials.

The MIC data from surveillance and clinical trials for *S. aureus* including methicillin resistant isolates, *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae, Streptococci viridans group* and *E. faecalis* showed similar distributions. The dalbavancin MIC90 from DUR001-301, -302 and -303 trials were ≤ 0.12 µg/mL.

In trial DUR001-303, there were no isolates with MIC values≥ 0.25 µg/mL. The isolates with dalbavancin MICs ≥ 0.25 µg/mL were identified in trials DUR001-301 and 302 with clinical outcome data only available for two patients. The MIC values for all the non-susceptible isolates from studies DUR001-301 and DUR001-302 isolates were retested as 0.06 µg/mL. From surveillance studies, about 20% of the non-susceptible isolates with MICs ≥ 0.25 µg/mL remained non-susceptible when retested. No correlation was observed between baseline dalbavancin MIC and clinical outcome in trials DUR001-301, - 302, and 303.

Medical reviewer's Comment: The microbiology reviewer concluded that clinical and surveillance studies data support a susceptible breakpoint of ≤0.12 µg/mL for Staphylococcus aureus (including methicillin-resistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group (including S. anginosus, S. intermedius, S. constellatus), and vancomycin-susceptible isolates of Enterococcus faecalis . The non-clinical and clinical PK/PD target attainment analyses support a breakpoint of ≤ 0.25 µg /mL. At the time this review was written a susceptible breakpoint of ≤ 0.25 µg /mL was proposed for all isolates listed in the dalbavancin package insert but the discussion of breakpoint determination was ongoing. For additional detail the reader is referred to microbiology review provided by Dr. Kalavati Suvarna.

4.3 Preclinical Pharmacology/Toxicology

No additional toxicology studies were submitted in support of this supplemental NDA. Animal toxicology studies to support the clinical investigation and registration of dalbavancin were conducted in rats, dogs, and rabbits. The preclinical findings in general toxicology studies in adult and juvenile rats and dogs consisted of 4 general responses: transient infusion reactions (observed only in dogs); local skin and vascular toxicity at the injection site (observed in rats and dogs); cytoplasmic vacuoles and/or pigment in multiple tissues in rats and dogs.
The liver and kidney were the principal target organs to evaluate toxicity in rats and dogs.

Overall, the major toxicities found by toxicology studies of dalbavancin were as follows:

- Liver toxicity in rats and dogs
- Renal toxicity in rats and dogs
- Local injection site reactions in rats and dogs
- Infusion related reactions in dogs (transient, dose dependent)
- Abortions in rabbits

At no observed adverse effect level (NOAEL) doses, the exposure levels in animals are equivalent to those in humans.

Liver Toxicity

- Observed at doses from 5-7 times the expected human dose on an exposure basis;
- AST and ALT elevations were observed earlier than histologic changes and persisted after histologic findings had reversed. Thus, transaminase elevation in dogs persisted in the dog for more than 15 months after the end of the treatment period;
- Histologic changes included dose-dependent hepatocellular necrosis;
- Liver toxicity was reversible, but residual hepatic fibrosis was observed after administration of 40 mg/kg/day, or 13 times the human dose on an exposure basis, for 90 days in dogs.

Renal Toxicity

- Observed at doses from 5-7 times the expected human dose on an exposure basis;
- Dose-dependent histologic changes included tubular necrosis, interstitial inflammation, and glomerulonephritis.

Systemic Infusion Reactions

- Acute or repeated IV infusion of dalbavancin in dogs associated with dose-dependent infusion reaction during or immediately following infusion, characterized by facial and/or paw skin swelling and redness, mucosal pallor, salivation, vomiting, sedation, and modest declines in blood pressure and increases in heart rate;
- Observed in all toxicology studies in dogs where the infusion period was ≤11 minutes and in all safety pharmacology studies in dogs where the infused dose was ≥30 mg/kg. Observed predominantly at doses 15-20 times the human dose on a mg/kg/day;
- Resolved within 1-hour post-dosing;
- Attributed to histamine release

Injection Site Toxicity

- Characterized by local skin swelling that corresponded to microscopic perivascular inflammation, fibrosis and vascular thrombosis;
- Dose-dependent in incidence and severity and observed at all dose levels after repeated administration;
- Reversible with cessation of dosing.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The Applicant reports that dalbavancin was found to be non-genotoxic in the bacterial reverse mutation assay and mammalian test systems for gene mutation in Chinese hamster lung (CHL) fibroblasts or by cytogenetic evaluation of chromosomal damage in Chinese hamster ovary (CHO) cells. An in vivo mouse micronucleus assay was also negative at clinically-relevant exposures.

In brief, the toxicological effects of dalbavancin at clinically relevant doses reflects injection site reactions and dose-related, partially-reversible, hepatic and renal toxicity, associated with slow systemic elimination with repeated dosing. The plasma exposures in animals at the NOAELs in repeat-dose toxicity studies 28 or 90 days long (b) (4)

The only adverse finding observed at exposures comparable to clinical exposure was the occurrence of abortions in rabbits due to maternal toxicity.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Dalbavancin, a semisynthetic lipoglycopeptide, interferes with cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking. Dalbavancin is bactericidal *in vitro* against *Staphylococcus aureus* and *Streptococcus pyogenes* at concentrations similar to those sustained throughout treatment in humans treated according to the recommended dosage regimen.

4.4.2 Pharmacodynamics

The antibacterial activity of dalbavancin appears to best correlate with the ratio of area under the concentration-time curve (AUC) to minimal inhibitory concentration (MIC) for *Staphylococcus aureus* based on animal models of infection. Consistent with its mechanism of action, involving interruption of cell wall synthesis, dalbavancin is bactericidal. In vitro killing by dalbavancin is best described as time-dependent. Most minimum bactericidal concentrations (MBC) and time-kill studies have been directed at staphylococci and streptococci, in particular, species that are relevant to ABSSSI... MIC ranges were observed to be very narrow and MIC90s for staphylococci were most often between 0.06–0.12 mg/L using validated broth micro dilution methods, and ≤0.03-0.06 mg/L against streptococci.

4.4.3 Pharmacokinetics

Dalbavancin pharmacokinetic (PK) parameters have been characterized in healthy subjects, patients, and specific populations. Dalbavancin pharmacokinetic (PK) parameters

have been characterized in healthy subjects, patients, and specific populations. The applicant has conducted Population-PK (popPK) analysis which included PK samples from DUR001-303. The results from the popPK analysis were used to assess the relationship between dalbavancin exposure and the primary (clinical response at 48-72 hours) and three secondary endpoints. Simulations based on the popPK model were also used to assess pharmacodynamic target attainment for various MIC levels.

Distribution
A maximum concentration of dalbavancin in plasma is achieved immediately following the end of infusion. Dalbavancin distributed into a steady-state volume of distribution (Vss) of 14 L. The protein binding measured in human plasma was 93%.
The disposition of dalbavancin is triphasic. The dalbavancin plasma concentration-time profile was defined in clinical study VER001-19, which provided the best estimate of dalbavancin disposition, sampling the concentration-time profile through 10 weeks.
The initial distributive phase (alpha phase) was short (t1/2 of approximately 2.5 hours). An elimination phase (beta phase) followed that accounted for the majority of drug elimination (t1/2 ~ 5 days). In patients, the predominant elimination rate was characterized by a t1/2 of 8.5 days. The terminal elimination phase characterizes the lower concentrations (<10 mg/L) at later times in the concentration-time curve (>28 days).

Metabolism
Dalbavancin is not a substrate, inducer, or inhibitor of cytochrome P450 isoenzymes.
No significant amounts of metabolite have been observed in human plasma, however a minor dalbavancin metabolite has been observed in human urine. In humans, a total of 8 to 12% of the administered dose is excreted as OH-dalbavancin in urine.

Excretion
Dalbavancin is excreted as intact drug and OH-dalbavancin in urine and as intact drug in feces. The estimated fraction of drug excreted unchanged in the urine is 33% of the administered dose (Study VER001-10, Module 5). The estimated amount of metabolite excreted in the urine is 12% of the total dose.

Specific Populations
Renal and Hepatic Impairment: Dalbavancin is eliminated by both renal and non-renal pathways**.** Dosage adjustment is not required for mild to moderate renal impairment or subjects receiving regularly scheduled dialysis. Based on the PK parameters and simulations, a dosage adjustment (25% dose reduction is recommended for patients with severe renal impairment who do not receive regular dialysis. No dosage adjustment of dalbavancin is required for patients (b) (4) of hepatic impairment. Dalbavancin showed good penetration into the extracellular fluid in skin tissue.

Gender: Clinically significant gender-related differences in dalbavancin PK have not been observed either in healthy subjects or in patients with infections. No dosage adjustment is recommended based on gender.

Geriatric Patients: Clinically significant age-related differences in dalbavancin PK have not been observed in patients with infections. No dosage adjustment is recommended based solely on age.

Pediatric Patients: The PK of dalbavancin in pediatric populations <12 years of age have not been established. As indicated in the description of dalbavancin PMRs provided in this review, a final report of a Phase 1 PK study in children aged 3 months to < 12 years is expected by March 2016.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 Phase 2 and Phase 3 Dalbavancin Trials Included in the Clinical Review

Trial/ Duration	Design	Type	Indication	Dalbavancin Dose	Dalbavancin	Comparator
VER001-4 APR 2002 – SEP 2003	Phase 2, randomized, open label vs. vancomycin	Safety Efficacy PK/PD	CRBSI with Gram-positive pathogens	***Grp A:*** 1000 mg on day 1, 500 mg on Day 8. ***Grp B:*** 650 mg on day 1, 65 mg on days 2–14 (this arm was discontinued). ***Grp C***: IV vancomycin: 1000 mg q12h or dose adjusted for renal impairment. Could switch to IV nafcillin/ oxacillin 2 g q4hor q6h after pathogen identification and susceptibility.	**40**	**34**
VER001-5 JUL 2001-JUN 2002	Phase 2, randomized, open label (1:1:1)	Safety Efficacy	cSSSI	***Arm 1:*** 1100 mg (single dose) on day 1 ***Arm 2:*** 1000 mg on day 1, 500 mg on day8 ***Arm 3:*** Standard antibiotics therapy	**41**	**21**
VER001-8 DEC 2002-JUN 2004	Phase 3, randomized double blind vs cefazolin (2:1)	Safety Efficacy	uSSSI	***Gr A:*** Dalbavancin 1000 mg on day 1, with option to follow 500 mg on day 8, possible switch to oral Placebo q6h. ***Gr B:*** IV cefazolin: 500 mg q8h, possible switch to oral cephalexin 500 mg q6h.	**367**	**186**
VER001-9 JAN 2003 – MAY 2004	Phase 3, randomized, double blind study (2:1)	Safety Efficacy	cSSSI	***Gr A:*** Dalbavancin1000 mg on day 1,500 mg on day 8, possible switch to oral placebo q12h ***Gr B:*** IV linezolid: 600 mg q12h, possible switch to oral linezolid 600 mg q12h	**571**	**283**

VER001-16 OCT 2003 – MAY 2004	Phase 3 open label, randomized study with comparator vancomycin (2:1)	Safety Efficacy	cSSSI or uSSSI	***Gr A:*** Dalbavancin 1000 mg on day 1, 500 mg on day 8. ***Gr B:*** IV vancomycin 1000 mgq12h; after 24 hours possible switch to oral cephalexin 500 mg -1 g q8h if pathogen was susceptible	**107**	**49**
DUR001-301 APR 2011 – NOV 2012	Phase 3, randomized, double-blind, double dummy (1:1)	Safety Efficacy	ABSSSI	***Gr A:*** IV dalbavancin 1000 mg, or dose-adjusted for CrCl on day 1, 500 mg, or dose-adjusted for CrCl on day 8 ***Gr B:*** IV vancomycin 1000 mg q12h, or dose-adjusted for renal impairment for 14 days; possible switch to oral therapy after 3 days to linezolid 600 mg q12h.	**284**	**284**
DUR001-302 SEP 2011-JAN 2013	Phase 3, randomized, double-blind, double dummy (1:1)	Safety Efficacy	ABSSSI	***Gr A:*** Dalbavancin 1000 mg, or dose-adjusted for CrCl on day 1, 500 mg, or dose-adjusted for CrCl on day 8 ***Gr B:*** IV vancomycin 1000 mg q12h, or dose-adjusted for renal impairment for 14 days; possible switch to oral therapy after 3 days to linezolid 600 mg q12h.	**368**	**367**
DUR001-303 APR 2014 – MAR 2015	Phase 3b, Double-Blind, Multicenter, Randomized, Active controlled (1:1)		ABSSSI ***Single Dose***	***Gr A:*** Dalbavancin 1500 mg single dose	**349****	
			Two-Dose	***Gr B:*** Dalbavancin 1000mg on day 1 and 500 mg on day 8	**346****	
Total Number of Subjects randomized in the above Trials					**2473**	**1233**

CRBSI: Catheter related blood stream infections; cSSSI: Complicated skin and soft tissue infections; uSSSI: Uncomplicated skin and soft tissue infections; ABSSSI: Acute Bacterial Skin and Skin Structure Infections;
** Both Arms in 303 received dalbavancin (different dosage regimens)
Note: Studies included in the integrated safety analysis are presented in the table.

Source: Adapted and partially modified from CSR, Module 5.2

5.2 Review Strategy

This sNDA includes data from a Phase 3b, double-blind, multicenter, randomized trial to compare the efficacy and safety of 1500 mg single dose dalbavancin to the currently approved two-dose regimen of dalbavancin for the treatment of ABSSSI, trial DUR001-303. The efficacy analyses of the review are focused on the results of this trial. The clinical safety data includes the trial DUR001-303 and supportive data pooled from prior seven phase2/3 studies.

As a part of this review, the phase 1 PK trial was reviewed in detail by Dr. Yang He, Pharm.D. Other relevant areas of the review have been deferred to discipline specific reviewers, such as Microbiology, Pharmacology/Toxicology, Statistics and CMC. For the detailed review of clinical trials included in the previous submission cycles of NDA 21883 the reader is referred to the Safety Review by Dr. Menfo Imoisili, Efficacy Review by Dr. Janice Pohlman from September 2005 (Legacy studies), and Clinical review by Dr. Dmitri Iarikov from September 2013 (Pivotal studies in ABSSSI, DUR001-301 and DUR001-302).

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial DUR001-303

The following section outlines the protocol for this study.

Study title
DUR001-303 trial was a Phase 3b, Double-Blind, Multicenter, Randomized Study to Compare the Efficacy and Safety of Single Dose (1500 mg) dalbavancin to a Two Dose Regimen (1000 mg on day 1 followed by 500 mg on day 8) of dalbavancin for the treatment in patients with known or suspected gram positive acute bacterial skin and skin structure infections (ABSSSI).

Study dates
April 18, 2014 to March 11, 2015

Study sites
The study was conducted in 60 sites including North America (US), South Africa, and Europe (Croatia, Georgia, Estonia, Hungary, Latvia, Russia, Romania, Serbia, and Ukraine)

Objectives/Rationale
Primary Objectives

The primary objective of this study was to compare the efficacy of treatment with a single dose of dalbavancin 1500 mg to treatment with a two-dose regimen of dalbavancin (1000 mg on day 1 followed by 500 mg on day 8) in patients with known or suspected gram-positive ABSSSI at 48 to 72 hours after the initiation of treatment.

Secondary Objectives
The secondary objectives of this study were as follows:

- To compare the efficacy outcomes at relevant time points as well as the safety profile of treatment with a single dose of dalbavancin versus the safety profile of treatment with a two dose regimen of dalbavancin in patients with known or suspected gram-positive ABSSSI.

- To compare the population PK profiles of a single dose of dalbavancin versus the two dose regimen of dalbavancin in patients with ABSSSI and to estimate and compare the PK/PD relationship of each dose regimen. Results for this objective, which was considered a sub-study is discussed in detail in clinical pharmacology review by Dr Yang He.

Study Design and Plan
Adult patients were randomly assigned in a 1:1 ratio to the following treatment groups:

- Single dose dalbavancin group received a single dose of dalbavancin IV on day 1, and a dalbavancin-matching placebo IV on day 8. The dalbavancin dose on day 1 was 1500 mg for patients with creatinine clearance (CrCl) ≥30 mL/min, and for patients with CrCl <30 mL/min who were receiving regular hemodialysis or peritoneal dialysis. In patients with CrCl <30 mL/min who were not receiving regular hemodialysis or peritoneal dialysis, the dalbavancin dose was 1000 mg on day 1.
- Two dose dalbavancin groups received the first dose of dalbavancin IV on day 1, and the second dose of dalbavancin IV on Day 8. The dalbavancin doses were 1000 mg on day 1 and 500 mg on Day 8 for patients with CrCl ≥30 mL/min, or for patients with CrCl <30 mL/min who were receiving regular hemodialysis or peritoneal dialysis. In patients with CrCl <30 mL/min who were not receiving regular

hemodialysis or peritoneal dialysis, the dalbavancin doses were 750 mg on day 1 and 375 mg on day 8.

The study design is depicted in
Figure 2

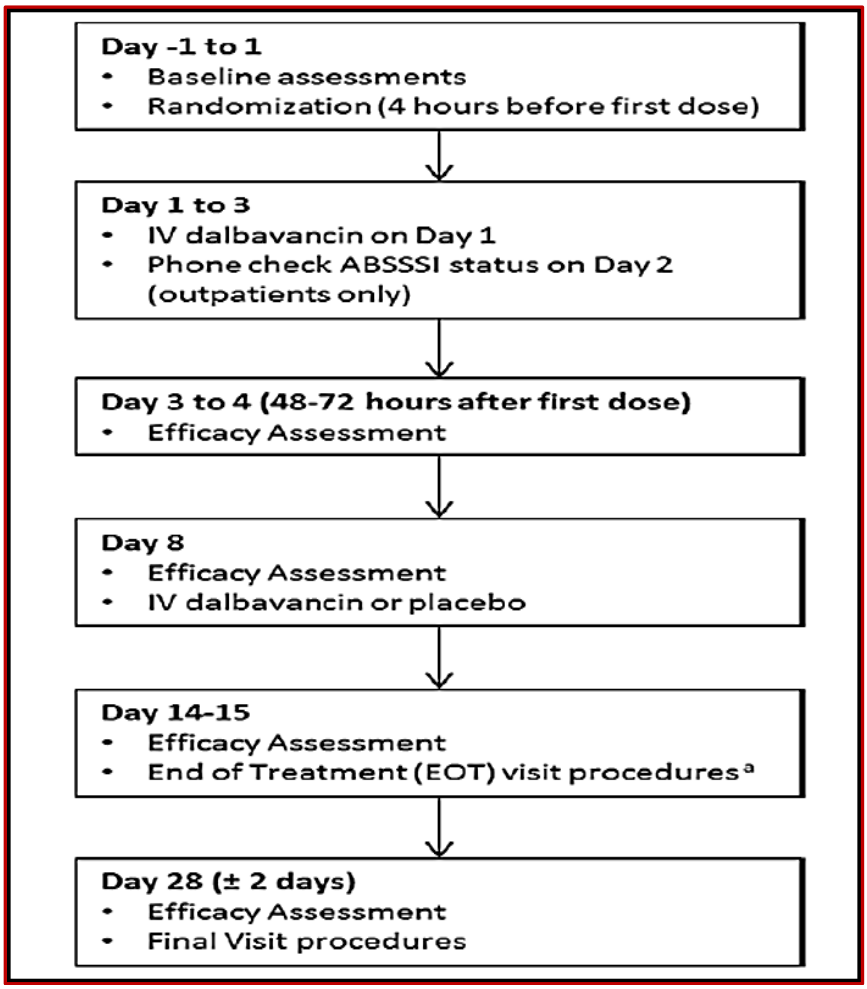

Figure 2 Protocol DUR001-303 Study Design (Source: Clinical Study Report, Figure 1)

a. If treatment was prematurely discontinued, the EOT visit was scheduled within 3 days of discontinuation.
Note: Safety assessments were performed at every visit.

5.3.1.1 Schedule of Assessments and Procedures

The schedule of assessments and procedures for all study visits is summarized in **Figure 3** below**.**

The study procedures were to be conducted at baseline and at a series of 6 time points thereafter. Treatment was to begin on day 1; baseline assessments were performed within 24 hours before the first dose of study drug, and patients were administered the first dose of study drug within 4 hours of randomization.

On day 2, patients being treated on an outpatient basis were contacted by the investigator to check for worsening of the presenting ABSSSI lesion. Efficacy assessments were performed on day 3-4; on day 8, at which patients were also administered the second dose of study drug; on day 14-15, which was defined as the EOT visit; and on day 28, which was defined as the Final Visit. Safety assessments were performed at every visit.

Visit:	Baseline	Day 1	Day 2	Day 3-4	Day 8	EOT	Final
Informed Consent	X						
Medical History and Demographics	X						
Complete Physical Examination	X						
Brief Physical Examination				X		X	X
Vital Signs [a]	X	X		X	X	X	X
Hematology	X			X		X	
Serum Chemistry	X			X		X	
hs-CRP level	X						
Serum lactate level	X						
Pregnancy testing/FSH [b]	X					X	
Banked serum	X						
Infection site specimen collection [c]	X						
Peripheral blood culture [d]	X						
Infection Site Assessment [e]	X			X	X	X	X
Patient contact			X[f]				
Pain Scale Assessment	X		X	X	X	X	X
Photograph (or tracing) of ABSSSI lesion	X			X		X	X
Previous Drug and Non-drug Treatments	X						
Concomitant Medications	X	X		X	X	X	X

Concomitant Non-drug Adjunctive Therapy	X	X		X	X	X	X
Study Drug Administered		X			X		
Clinical Status				X	X	X	X
Investigator Assessment of Clinical Outcome				X	X	X	X
Resource utilization						X	X
SSTI-Convenience Questionnaire						X	
Adverse Events	X	X	X[f]	X	X	X	X
Optional PK sampling [g]		X	X	X			

EOT = End of treatment visit; hs-CRP = High sensitivity C-reactive protein; FSH = follicle-stimulating hormone; ABSSSI = Acute bacterial skin and skin structure infection; SSTI = Skin and soft tissue infection; PK = Pharmacokinetic.

[a] Vital signs included blood pressure, respiration rate, pulse rate, and temperature (oral, rectal, tympanic, or core). The measurement of temperature to satisfy entry criteria was required to be a body temperature measured by the patient/caregiver or investigator within 24 hours of first dose. Height and weight were obtained at baseline only.

[b] Pregnancy test (women of childbearing potential) or serum FSH (to confirm post-menopausal status for women <50 years of age or those ≥50 years of age who have been post-menopausal for <2 years) was to be performed as required by the protocol.

[c] If an exudate/aspirate/pus sample could be obtained, it was to be cultured by the local laboratory, which was also to conduct organism identification and antibiotic susceptibility testing.

[d] Blood cultures were to be drawn at Baseline (prior to study drug treatment) from 2 different anatomical sites and not through an existing intravascular line. If positive, blood cultures were to be repeated immediately until negative.

[e] Includes assessment for presence or absence of local signs of ABSSSI, plus measurement of the ABSSSI lesion. The infection site assessment at Baseline was required to be performed in a time window beginning 4 hours prior to and ending 3 hours after the first dose of study drug.

[f] Day 2 contact and AE collection applied only to patients being treated as outpatients.

[g] PK sampling was to occur at 1 hour (±30 min), 18 hours (±2 hours), 23 hours (±4 hours), and 36-48 hours for patients in the PK substudy.

Figure 3, Schedule of Assessments and Procedures (Source: Clinical Study Report, Table 2)

All patients who discontinued treatment with study drug, for any reason, were encouraged to complete the trial, and at minimum were to have a final study visit within 3 calendar days after discontinuation, at which all EOT visit procedures were performed. Such patients were also requested by the investigator to return for a Final Visit on day 28. The investigator was required to follow up with the patient through day 28 regarding any unresolved adverse events whether or not this Final Visit occurred.

5.3.1.2 Selection of Study Population

Inclusion Criteria

Each patient was required to meet all of the following criteria to be eligible for the study:
1. Male or female patients, 18-85 years of age.

2. A personally signed and dated informed consent document indicating the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

3. All patients were required to have ABSSSI (suspected or confirmed to be caused by Gram-positive bacteria) defined for purposes of this study as an infection (major cutaneous abscess, surgical site or traumatic would infection or cellulitis) 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 is accompanied by erythema, edema and/or induration which:

i. required surgical incision and drainage (I&D), and
ii. was associated with cellulitis such that the total affected area involved at least 75 cm^2 of erythema, and
iii. was defined by a margin of erythema that was ≥5 cm from the rim of induration or edema that defines the border of the abscess in all directions, or,
iv. 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 is associated with cellulitis such that:

i. the total affected area involved at least 75 cm^2 of erythema, and
ii. was defined by a margin of erythema in at least one direction that was ≥5 cm
iii. from the edge of the wound, or
iv. 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 one 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:

i. was associated with erythema that involved at least 75 cm^2 of surface area, or
ii. 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 two of the following signs of ABSSSI:

a. Purulent drainage/discharge
b. Fluctuance
c. Heat/localized warmth
d. Tenderness to palpation
e. Swelling/induration

5. All patients were required to present with at least ONE of the following systemic signs of infection:

a. An elevated body temperature ≥38°C/100.4°F as measured by the patient/caregiver or investigator within 24 hours of baseline;
b. White blood cell count >12,000 cells/mm^3;
c. A manually performed white blood differential count with ≥10% band forms, regardless of peripheral white blood cell count.

6. All patients were required to be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria
Patients who met any of the following criteria were excluded from the study:

1. Patients with a contra-indication to the administration of dalbavancin such as hypersensitivity to any of the glycopeptide agents.

2. Females of child-bearing 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 mmHg for more than 2 hours despite adequate fluid resuscitation, with evidence of hypo-perfusion or need for sympathomimetic agents to maintain blood pressure.

4. Participation in another study of an investigational drug or device within 30 days prior to enrollment

5. Receipt of a systemically administered antibiotic with a Gram-positive spectrum that achieves therapeutic concentrations in the serum or at the site of the ABSSSI within 14 days prior to randomization. An exception was allowed for patients receiving a single dose of a short-acting (half-life ≤12 hours) antibacterial drug prior to randomization; up to 25% of patients may have received such therapy.

6. Infection due to an organism known prior to study entry to be resistant to dalbavancin or vancomycin (vancomycin MIC >8 µg/mL).

7. Patients with evidence of meningitis, necrotizing fasciitis, gas gangrene, gangrene, septic arthritis, osteomyelitis; endovascular infection, such as clinical and/or echocardiographic evidence of endocarditis or septic thrombophlebitis.

8. Infections caused exclusively by Gram-negative bacteria (without Gram-positive bacteria present) and infections caused by fungi, whether alone or in combination with a bacterial pathogen.

9. Venous catheter entry site infection.

10. Infections involving diabetic foot ulceration, perirectal abscess or decubitus ulcer.

11. Patient with an infected device, even if the device is removed. Examples include infection of: prosthetic cardiac valve, vascular graft, a pacemaker battery pack, joint prosthesis, hemodialysis catheter, implantable pacemaker or defibrillator, intra-aortic balloon pump, left ventricular assist device, a peritoneal dialysis catheter, or a neurosurgical device such as a ventricular peritoneal shunt, intra-cranial pressure monitor, or epidural catheter.

12. Gram-negative bacteremia, even in the presence of gram-positive infection or gram positive bacteremia. Note: If gram-negative bacteremia developed during the study, or was subsequently found to have been present at baseline, the patient was to have been removed from study treatment and was to receive appropriate antibiotic(s) to treat the gram-negative bacteremia. Such patients were to have had an EOT visit performed within 3 calendar days after discontinuing study drug, but were required to have adverse events reported through the Final Visit.

13. Patient's 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 defined as any of the following criteria: absent or abnormal Doppler wave form, toe blood pressure of <45 mmHg, ankle-brachial index <0.5, and/or critical ischemia as assessed by a vascular surgeon.

15. Patients with ABSSSI such as superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that required only surgical drainage for cure.

16. Concomitant condition requiring any antibiotic therapy that would interfere 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 (defined as procedures conducted under sterile technique and typically unable to be performed at the bedside) for the ABSSSI, or patients who were expected to require more than 2 such interventions.

20. Medical conditions in which chronic inflammation may preclude assessment of clinical response to therapy even after successful treatment (e.g., chronic stasis dermatitis of the lower extremity).

21. Absolute neutrophil count <500 cells/mm^3.

22. Known or suspected human immunodeficiency virus (HIV)-infected patients with a CD4 cell count <200 cells/mm^3 or with a past or current acquired immunodeficiency syndrome (AIDS)-defining condition and unknown CD4 count.

23. Patients with a recent bone marrow transplant (in post-transplant hospital stay).

24. Patients receiving oral steroids >20 mg prednisolone per day (or equivalent) or receiving immunosuppressant drugs after organ transplantation.

25. Patients with a rapidly fatal illness, who were not expected to survive for 3 months.

26. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

27. Prior participation in this study.

For the duration of the study, all female patients of child-bearing potential and all male patients agreed to be strictly abstinent from sexual intercourse with any individual of the opposite sex, or to follow the instructions for contraception.

Medical Reviewer's Comment: The trial design and inclusion/exclusion criteria for the study were appropriate and consistent with the FDA guidance on the design of ABSSSI trials.[1] Moreover, the protocol was the subject of Special Protocol Assessments.

[1] Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment, October 2013. htpp://www fda.gov/downloads/Drugs/…/Guidances/ucm071185.pdf

5.3.1.3 Treatments

Patients were randomly assigned in a 1:1 ratio to either the single-dose dalbavancin group or the two-dose dalbavancin group. The schedule of dosing for patients with CrCl ≥30 mL/min or for patients with CrCl <30 mL/min who were receiving regular hemodialysis or peritoneal dialysis was as follows:

Table 3 Treatment Groups : Trial DUR001-303	
The schedule of dosing for patients with CrCl ≥30 mL/min	
Single-Dose Group	**Two-Dose Group**
Day 1: 1500 mg IV dalbavancin administered over 30 minutes Day 8: Dalbavancin-matching placebo IV administered over 30 minutes	Day 1: 1000 mg IV dalbavancin administered over 30 minutes Day 8: 500 mg IV dalbavancin administered over 30 minutes
The schedule of dosing for patients with CrCl <30 mL/min who were not receiving regular hemodialysis or peritoneal dialysis	
Single-Dose Group	**Two-Dose Group**
Day 1: 1000 mg IV dalbavancin administered over 30 minutes Day 8: Dalbavancin-matching placebo IV administered over 30 minutes	Day 1: 750 mg IV dalbavancin administered over 30 minutes Day 8: 375 mg IV dalbavancin administered over 30 minutes

5.3.1.4 Method of Assigning Patients to Treatment Groups

A patient was eligible for randomization once it was determined that he or she met all of the inclusion criteria and none of the exclusion criteria. Randomization was stratified by geographic region, infection type (major abscess, cellulitis, or traumatic wound/surgical site infection), and prior use of antibiotics for ABSSSI:

- At least 20% of patient enrollment was required to be at study sites in the US;
- Enrollment of patients with major abscess as the presenting ABSSSI infection type was to be capped at no more than 30% of total patient enrollment, based on categorization of infection type at time of randomization and recognizing that the infection type may evolve over time;
- No more than 25% of patients were to have received prior antibiotic therapy for the presenting ABSSSI, based on medical history available at the time of randomization.

5.3.1.5 Prohibited Antibacterial Medications

Concomitant treatment with systemic and topical antibacterial medications was prohibited during the study, up to the EOT visit, with the following exceptions:

- Vancomycin oral 125 mg or 250 mg every 6 hours was allowed in both treatment groups for the treatment of *Clostridium difficile* infection, as required throughout the duration of the study. The Sponsor did not provide oral vancomycin.

- Metronidazole IV or oral 500 mg every 8 hours was allowed in both treatment groups for the treatment of *Clostridium difficile* infection, as required throughout the duration of the study. The Sponsor did not provide metronidazole.
- Other antibacterial medications that do not achieve therapeutic levels in the serum (e.g., nitrofurantoin) or at the site of the ABSSSI lesion could have been considered; close consultation with the Sponsor's medical monitor was advised prior to use of these antibiotics.
- Patients who developed a gram-negative bacteremia during the study, or for whom gram negative bacteremia was subsequently found to have been present at baseline, were to be discontinued from treatment with study drug and receive appropriate antibiotic(s) to treat the gram-negative bacteremia, with follow-up study visits.
- Patients subsequently discovered to have had a gram-positive organism at baseline resistant to dalbavancin had the option to remain on study drug based on the investigator's impression of the patient's clinical response.

5.3.1.6 Adjunctive Antibacterial Medications

Adjunctive treatment for ABSSSI with systemic and topical antibacterial medications was prohibited during the study, up to the EOT visit, with the following exceptions:

- Metronidazole IV or oral 500 mg every 8 hours was allowed in both treatment groups for infection with suspected anaerobic pathogens, as required throughout the duration of the study.
- Aztreonam was allowed in both treatment groups for the treatment of ABSSSI caused by gram-negative bacteria, and was the only systemic antibacterial medication allowed for empiric treatment based on information available at the time of randomization. Empiric treatment with aztreonam post-randomization was not permitted, but use of aztreonam to treat an infection with a gram-negative bacterial species confirmed by culture was acceptable at any time during the study.

5.3.1.7 Non-Drug Adjunctive Therapy

The potential need for surgical intervention in patients with ABSSSI during the study was prospectively defined at baseline, and patients expected to require more than 2 surgical interventions for the ABSSSI lesion were enrolled. The following adjunctive therapies were permitted for the treatment of ABSSSI:

- Debridement at the bedside;
- Topical solutions including antiseptic agents such as povidine-iodine;
- Local bedside wound care as per hospital protocol.

Medical Reviewer's Comment: Because surgical incision and drainage might influence treatment outcomes among patients with major cutaneous abscesses, patients with major cutaneous abscesses were restricted to no more than 30 percent of the clinical trial population as mentioned in the FDA guidance on the design of ABSSSI trials.

5.3.1.8 Efficacy Endpoints

Primary Efficacy evaluation (Clinical response at 48-72 hours in ITT population)

The primary efficacy outcome measure was clinical response at 48 to 72 hours (decrease in > 20% of lesion area, relative to baseline measurement) post study drug initiation in the ITT population. The NI hypothesis test was a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the 95% CI for the difference in responder rates was found to be greater than -10%, then the single-dose dalbavancin regimen was to be declared non-inferior to the two-dose dalbavancin regimen.

The secondary efficacy evaluation (Clinical status at EOT and at Final Visit in CE and ITT population)

The secondary endpoints were clinical status at EOT (day 14-15) in the CE and ITT populations, and clinical status at the Final Visit (28 ±2 days after initiation of study drug) in the CE and ITT populations.

Although no formal NI hypothesis testing was planned, the statistical analysis for the secondary efficacy evaluation at the Final Visit included a comparison between treatment groups in the ITT population using a 95% CI threshold of -15%. No pre-specified NI margin was determined for CE population. Clinical success at the Final Visit was defined as a decrease in lesion area by ≥ 90% from baseline, the patient's temperature ≤ 37.6°C and local signs of infection no worse than mild.

The patients who received any rescue therapy for ABSSSI (except for antibiotics given for a non-ABSSSI indication), and those who died from any cause were considered non responders.

Medical Reviewer's Comment:
Medical Reviewer's Comment: Since in one of the registrational dalbavancin trials a lower clinical success rate at days 26-30 was observed in the dalbavancin arm, secondary efficacy endpoints evaluating the maintenance of treatment effect were specifically discussed during special protocol agreement deliberations to ensure that the efficacy is not compromised beyond the 48- 72 hour assessment. The Division recommended including a secondary efficacy evaluation at day 28 in the ITT population using a 95% CI threshold of 15% based on criteria provided above.

5.3.1.9 Protocol Amendments

Two amendments were made to the protocol.
Amendment 1, March 26, 2014
A secondary objective was added to introduce a population PK study in order to compare the population PK profiles of a single dose of dalbavancin 1500 mg versus the two dose

regimen of dalbavancin (1000 mg on day 1 followed by 500 mg on day 8) in patients with ABSSSI and to estimate and compare the PK/PD relationship of each dose regimen.

- Clinical laboratory tests were to be obtained at Baseline, day 3-4 and at day 14-15 or premature withdrawal instead of just baseline and day 28.
- Minor changes to the protocol included the option to dilute dalbavancin in glucose as well as dextrose, contact information for medical monitoring and safety purposes as well as clarification of statistical methodology.

Amendment 2, November 24, 2014

- Clarification was made to the definition of rescue antibacterial therapy as related to the primary endpoint.
- Clarification was provided related to the analysis populations for the secondary analyses.
- The protocol sample size was changed from 410 patients to 698 based on the observed response rate at the interim analysis.

Medical Reviewer's Comment: The Applicant discussed these issues with the division while the protocol was proceeding, and the division agreed to accept the revisions including the revised sample size. The protocol changes do not affect data interpretation and comparison between the 1500 mg single dose group with the two dose group.

5.3.1.10 Protocol Deviations

There were 105/349 patients (30.1%) in the single-dose group and 100/349 patients (28.7%) in the two-dose group who had important protocol deviations. The important protocol deviations that were most common in both treatment groups are listed below:

Visit Schedule, which includes deviations mostly related to occurrences when specific assessments within visits were completed outside protocol-specified time windows: 80 of the 139 important deviations (57.6%) in the single-dose group and 70 of the 131 important deviations (53.4%) in the two-dose group.

Tests and Procedures, which includes deviations mostly related to occurrences when complete visits or specific assessments within visits were missed or were completed by phone; this category may also include assessments done improperly: 37 of 139 important deviations (26.6%) in the single-dose group and 39 of the 131 important deviations (29.8%) in the two-dose group.

Medical Reviewer's Comment: Most commonly reported deviations in all randomized patients were related to the visit schedule. In the statistical analysis plan, major protocol deviations were predefined.

6 Review of Efficacy

6.1 Indication

This supplemental NDA supports the use of a single dose dalbavancin regimen for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of gram-positive bacteria.

6.1.1 Methods

The Applicant performed one clinical efficacy trial (DUR001-303), to support the claim for a single dose dalbavancin for the treatment of ABSSSI. DUR001-303 trial was a phase 3b, double-blind, multicenter, randomized, non-inferiority trial to compare the efficacy and safety of single dose (1500 mg)dalbavancin to a two dose regimen (1000 mg on day 1 followed by 500 mg on day 8) of dalbavancin for the treatment in patients with known or suspected gram positive ABSSSI. Details of this trial are discussed in section 5.3, Discussion of Individual Studies/Clinical Trials.

Efficacy analyses performed by both the Applicant and the Agency will be presented in this section. The Agency has no specific issue with the way in which the pre-specified analyses were conducted; however, different statistical models and imputation strategies were utilized by the Agency as sensitivity analyses to explore the robustness of the data. For full details of the sensitivity analyses, the reader is referred to the review by the Biometrics reviewer.

6.1.1.1 Analysis Populations

A total of 8 different patient populations were defined for statistical analysis in trial DUR001-303: the ITT population, a modified ITT (mITT) population that also serves as the safety population, microbiological ITT (microITT) and Microbiological modified ITT (micro-mITT) populations, 2 different clinically evaluable (CE) populations (CE-EOT and CE-Final Visit), and 2 different microbiologically evaluable (ME) populations (ME-EOT and ME-Final Visit). The proportions of patients in analysis populations were similar between two groups. The number of subjects, who were considered for the primary and secondary analyses in trial DUR001-303, is presented in **Table 4** below.

Table 4 Efficacy Analysis Population: DUR001-303

Analysis Population	Dalbavancin Single Dose N=349, n (%)	Dalbavancin Two Doses N=349, n (%)	Total N=698, n (%)
ITT Population	349/349 (100.0)	349/349 (100.0)	698/698 (100.0)
mITT Population	349/349 (100.0)	346/349 (99.1)	695/698 (99.6)
Safety Population	349/349 (100.0)	346/349 (99.1)	695/698 (99.6)
CE-EOT Population	302/349 (86.5)	302/349 (86.5)	604/698 (86.5)

CE-FV Population	271/349 (77.7)	267/349 (76.5)	538/698 (77.1)
MicroITT Population	210/349 (60.2)	220/349 (63.0)	430/698 (61.6)
Micro-mITT Population	210/349 (60.2)	220/349 (63.0)	430/698 (61.6)
ME-EOT Population	176/349 (50.4)	186/349 (53.3)	362/698 (51.9)
ME-FV Population	156/349 (44.7)	163/349 (46.7)	319/698 (45.7)
ITT = Intent-to-treat; mITT = Modified Intent-to-treat; CE = Clinically Evaluable; ME = Microbiologically Evaluable; MicroITT = Microbiological Intent-to-Treat; Micro-mITT = Microbiological modified Intent to treat; FV = Final Visit; EOT = End of treatment; N = Number of patients in the ITT population;			

Definition of Analysis Populations

ITT population: All randomized patients regardless of whether or not they received the study drug.

mITT population/ Safety population: All patients in the ITT population who received at least 1 dose of dalbavancin are included in the mITT population.

CE population: All patients from the mITT populations who were clinically evaluable at EOT or Final Visit. Two different CE populations are defined based on the timing of the outcome assessment to be evaluated: CE-EOT and CE-Final Visit.

Micro-mITT: All patients in the mITT population who also met criteria to be included in the microITT population.

ME population: Each ME population included only patients who qualified to be included in the microITT population and the respective CE population.

6.1.2 Demographics

6.1.2.1 The Baseline characteristics of ITT population

The baseline characteristics of the ITT population are presented in **Table 5**. The mean age of subjects in both groups was around 48 years. The mean BMI was 28.69 kg/m2 and 29.0 kg/m2, in single and two dose group respectively. Over 85% of subjects in both groups were <65 years old. Approximately 90% of subjects in both arms were White, whereas, African Americans represented roughly 8.5% of the study population in both arms. Over 15% of subjects were Hispanic or Latino. Slightly less than half of the patients in both arms were enrolled in the US sites, while the majority of patients were enrolled in Eastern Europe or South Africa. (**Table 5**)

Table 5 Demographics and Baseline Characteristics (ITT Population)			
	Dalbavancin Treatment Groups		
	Single Dose (N=349)	Two-dose (N=349)	Total (N=698)
Age (years)			
Mean	48.0 (14.8)	48.3 (14.7)	48.2 (14.8)
Median	49.0	50.0	49.5
Min, max	18, 85	19, 84	18, 85
Gender, n (%)			
Male	204 (58.5)	203 (58.2)	407 (58.3)
Female	145 (41.5)	146 (41.8)	291 (41.7)
Race, n (%)			
White	312 (89.4)	311 (89.1)	623 (89.3)
Black or African American	28 (8.0)	31 (8.9)	59 (8.5)
Native Hawaiian or other Pacific	1 (0.3)	0	1 (0.1)
Asian	3 (0.9)	1 (0.3)	4 (0.6)
American Indian or Alaska Native	4 (1.1)	1 (0.3)	5 (0.7)
Other	1 (0.3)	5 (1.4)	6 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	51 (14.6)	60 (17.2)	111 (15.9)
Not Hispanic or Latino	289 (82.8)	283 (81.1)	572 (81.9)
Not Reported	9 (2.6)	5 (1.4)	14 (2.0)
Unknown	0	1 (0.3)	1 (0.1)
BMI (Kg/m^2)			
n	349	349	698
Mean (SD)	28.69 (7.45)	29.00 (7.30)	28.85 (7.37)
Median	26.90	27.80	27.20
Min, max	15.9, 70.6	17.9, 65.5	15.9, 70.6
BMI category			
<25 kg/m2	115 (33.0)	122 (35.0)	237 (34.0)
25 to 30 kg/m2	123 (35.2)	99 (28.4)	222 (31.8)
>30 kg/m2	111 (31.8)	128 (36.7)	239 (34.2)
Cr CL (mL/min)			
n	349	347	696
Mean (SD)	96.68 (36.166)	94.91 (36.390)	95.80 (36.262)
Median	92.81	93.34	92.98
Min, max	12.4, 232.3	17.2, 198.5	12.4, 232.2
Cr CL category, n/N (%)			
<30 mL/min	2/349 (0.6)	7/347 (2.0)	9/696 (1.3)
≥30 mL/min	347/349 (99.4)	340/347 (98.0)	687/696 (98.7)
Geographic Region			
United States	158 (45.3)	160 (45.8)	318 (45.6)
Rest of World *	191 (54.7)	189 (54.2)	380 (54.4)

SD = Standard deviation; CrCl: Creatinine clearance; BMI = body mass index.
** Includes Croatia, Georgia, Estonia, Hungary, Latvia, Romania, Russia, Serbia, South Africa and Ukraine.*
Source: Clinical Study Report, Table 6, Trial DUR001-303

Medical Reviewer's Comment: The numbers of subjects in both treatment arms were balanced. The study population was also balanced between two arms in terms of age, gender, body mass index and baseline creatinine clearance. There were more male patients in both arms.

6.1.2.2 Infection type, Infection type by geographic region, and Location and Size of infections for the ITT population

Table 6 below summarizes infection type, infection type by geographic region, and prior use of antibacterial drugs for the ITT population.

The most common infection type overall was cellulitis (47.4%), followed by wound infection (26.9%) and major abscess (25.6%). The proportions of patients with infections of these respective types were similar across treatment groups, (**Figure 4**). However, major abscess was the most common infection type in patients enrolled in the US (39.6%) whereas cellulitis was the most common infection type in the sites located elsewhere(62.9%).

Most common location of infection was lower extremities (slightly over 40% in both groups), followed by arm (about 20% in both groups), and buttocks (about 12% in both groups).

Table 6 Infection Type, Infection Type by Geographic region, Prior Use of Antibiotics, and Primary Infection Site (ITT population)

	Dalbavancin Treatment Groups		
	Single Dose (N = 349)	**Two-dose (N = 349)**	**Total (N = 698)**
Infection Type			
Cellulitis	165 (47.3)	166 (47.6)	331 (47.4)
Major abscess	88 (25.2)	91 (26.1)	179 (25.6)
Wound infection (surgical site, traumatic)	96 (27.5)	92 (26.4)	188 (26.9)
Prior Use of Antibiotics			
Users	19 (5.4)	13 (3.7)	32 (4.6)
Non-Users	330 (94.6)	336 (96.3)	666 (95.4)
Geographic Region and Infection Type			
United States, N	158	160	318
Cellulitis	46 (29.1)	46 (28.8)	92 (28.9)
Major abscess	61 (38.6)	65 (40.6)	126 (39.6)
Wound infection (surgical site, traumatic)	51 (32.3)	49 (30.6)	100 (31.4)
Rest of World, N	191	189	380
Cellulitis	119 (62.3)	120 (63.5)	239 (62.9)
Major abscess	27 (14.1)	26 (13.8)	53 (13.9)
Wound infection (surgical site, traumatic)	45 (23.6)	43 (22.8)	88 (23.2)
Primary Infection Site			
Leg	151/ 349 (43.3%)	140/ 349(40.1%)	291/ 698(41.7%)
Arm	70/ 349 (20.1%)	78/ 349 (22.3%)	148/ 698(21.2%)
Buttock	43/ 349 (12.3%)	41/ 349 (11.7%)	84/ 698 (12.0%)

Foot	23/ 349 (6.6%)	18/ 349 (5.2%)	41/ 698 (5.9%)
Hand	15/ 349 (4.3%)	17/ 349 (4.9%)	32/ 698 (4.6%)
Abdomen	14/ 349 (4.0%)	18/ 349 (5.2%)	32/ 698 (4.6%)
Back	11/ 349 (3.2%)	13/ 349 (3.7%)	24/ 698 (3.4%)
Knee	14/ 349 (4.0%)	7/ 349 (2.0%)	21/ 698 (3.0%)
Head and/or Neck	8/ 349 (2.3%)	10/ 349 (2.9%)	18/ 698 (2.6%)
Chest	10/ 349 (2.9%)	7/ 349 (2.0%)	17/ 698 (2.4%)
Face	7/ 349 (2.0%)	9/ 349 (2.6%)	16/ 698 (2.3%)
Shoulder	3/ 349 (0.9%)	8/ 349 (2.3%)	11/ 698 (1.6%)
Groin	5/ 349 (1.4%)	4/ 349 (1.1%)	9/ 698 (1.3%)
ITT = Intent-to-treat ** Includes Croatia, Georgia, Estonia, Hungary, Latvia, Romania, Russia, Serbia, South Africa and Ukraine.* Source: Clinical study report, Table 5, DUR001-303, ISS module 5.3.5.3			

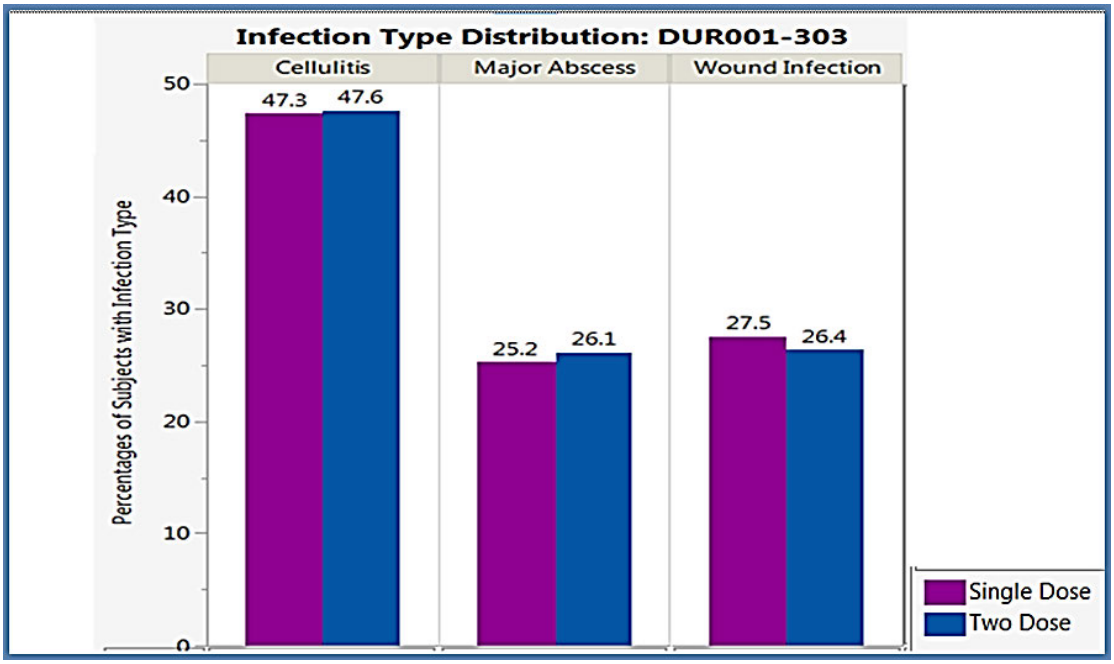

Figure 4 Distribution of three types of infection between two arms: DUR001-303 trial
(Source: FDA Medical Reviewer analysis)

Medical Reviewer's Comment: The proportions of subjects with three different types of infection were similar between two groups. However, there was an imbalance between the US and non-US trial sites in terms of infection type. Major abscess was the most common infection type in US sites, whereas cellulitis was the most common type in non-US sites. The reason for this difference is not clear. Overall in the trial less than 30% of patients had major abscess. About 5% of patients had previously used antibiotics for ABSSSI.

Lesion Size (cm^2)

The median lesion area was essentially equivalent in both groups, 296 cm^2 for the single dose group vs 293 cm^2 for the two-dose group. Cellulitis lesion areas were generally larger

(376 cm^2 vs 344 cm^2 in single and two dose group respectively) than lesions of major abscess (270 vs 261 cm^2 in single and two dose group respectively) and wound infection (257 vs 278 cm^2 in single and two dose group respectively). (
Figure 5)
Of note, there were 2 patients with lesion sizes <75 cm^2, both in the single-dose group and both with the presenting ABSSSI lesion located on the face, however it was qualified according to the inclusion criteria selected for lesion on the face, which was >50 cm^2 .

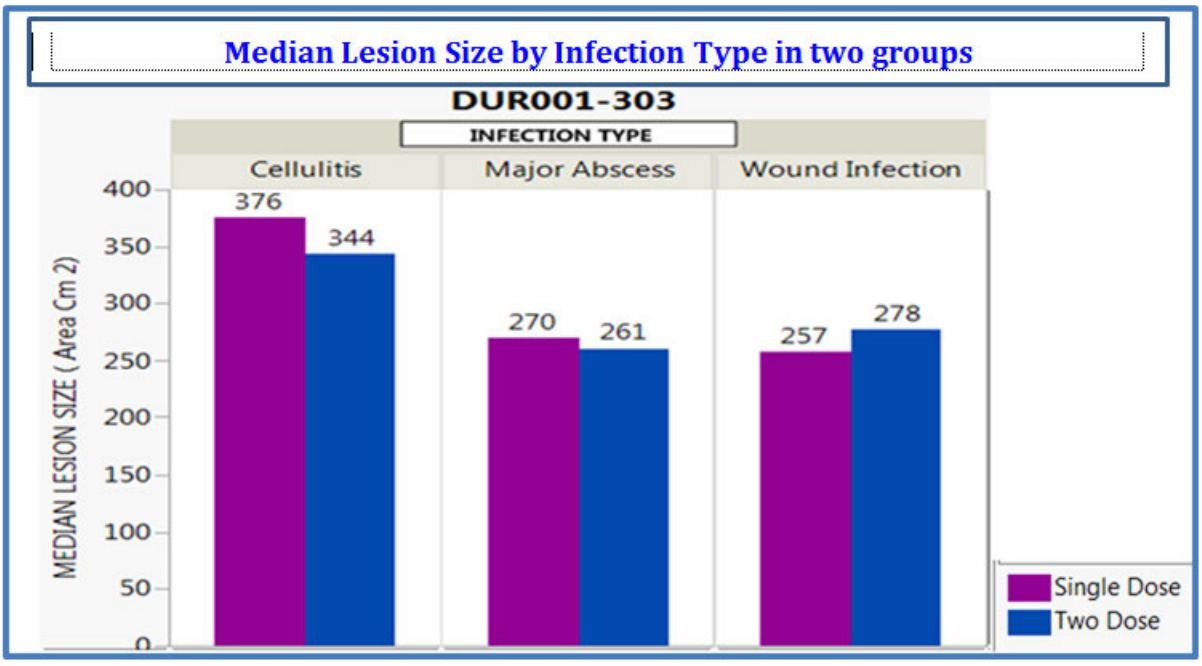

Figure 5 Median size of lesion in the single dose vs two-dose groups by infection type
(Source: FDA Medical Reviewer analysis)

Medical Reviewer's Comment: The size of the lesions was balanced between the two treatment groups in trial DUR001-303.

Each subject's pre-specified local signs and symptoms were recorded at baseline and these were evenly distributed between both treatment groups. The vast majority of subjects had baseline erythema (96.5% to 97.4%); heat/localized warmth (94.3% to 94.8%), tenderness to palpation, (96.3% to 97.4%), and swelling/induration (91.7% to 92.8%).
The other local signs which were commonly reported as absent or mild were fluctuance (61.3% to 61.9% of patients across treatment groups) and purulent drainage/discharge (56.2% to 62.8% of patients across treatment groups). These signs were more prevalent in patients with major abscess or wound infection as compared to those with cellulitis.

The proportions of patients with the various systemic signs of infection at baseline were generally similar across treatment groups. The majority of patients in the ITT population

had temperature of ≥38°Cat baseline (83.1% vs 81.6% of patients in single dose and two-dose group respectively). Over 40% of patients in both groups met the criteria for Systemic Inflammatory Response Syndrome (SIRS) at baseline (42.4% in the single-dose group and 44.4% in the two-dose group). The incidence of systemic signs of infection at study entry is provided in **Table 7** below.

Table 7 Systemic Signs of Infection at Baseline (ITT Population)		
	Dalbavancin Treatment Groups, n/N (%)	
	Single-Dose (N = 349)	**Two-Dose (N = 349)**
Total patients with ≥1 systemic sign of infection	349/349 (100)	343/349 (98.3)
Temperature ≥38°C	290/349 (83.1)	283/346 (81.6)
White blood cells >12,000/mm³	132/348 (37.9)	126/342 (36.8)
Bands ≥10%	56/263 (21.3)	46/268 (17.2)
Met SIRS criteria at baseline	148/349 (42.4)	154/347 (44.4)
SIRS = Systemic Inflammatory Response Syndrome, defined as having two or more of the following: Temperature <36°C or >38°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute; WBC count <4000 cells/mm³ or >12,000 cells/mm³ or >10% bands. Source: Clinical study report, Table 8, DUR001-303.		

Medical Reviewer's Comment: Baseline local and systemic signs of infection were similarly distributed between the two treatment arms.

6.1.2.4 Microbiological Assessment of the ABSSSI Infection site at Baseline

Approximately 95% of patients in DUR001-303 trial had ABSSSI microbiological specimen obtained. Specimens were most commonly obtained via needle aspiration in both treatment groups. **Table 8** below summarizes microbiological assessment for trial population.

Table 8 Microbiological Assessment of the ABSSSI Infection Site at Baseline (ITT Population)		
	Dalbavancin Treatment Group, n/N (%)	
	Single-Dose (N = 349)	**Two-Dose (N = 349)**
Total patients with ABSSSI specimen obtained	329/349 (94.3)	332/349 (95.1)
Total number of ABSSSI specimens obtained	342	344
Source of specimens		
Biopsy	37/342 (10.8)	35/344 (10.2)
Needle aspirate	137/342 (40.1)	138/344 (40.1)
Other *	25/342 (7.3)	29/344 (8.4)
Surgical swab	93/342 (27.2)	105/344 (30.5)
Wound scraping	42/342 (12.3)	31/344 (9.0)

Local laboratory		
Total number of specimens with Gram stain performed	330	338
Number of patients with specimen and Gram stain	324/349 (92.8)	332/349 (95.1)
Culture positive for pathogen	210/349 (60.2)	220/349 (63.0)
Central laboratory		
Total number of specimens with Gram stain performed	253	263
Number of patients with specimen and Gram stain	247/349 (70.8)	257/349 (73.6)
Culture positive for pathogen	205/349 (58.7)	208/349 (59.6)
* Includes purulent fluid taken by aseptic aspiration; specimens taken during curettage, debridement, or incision and drainage; scrapings from the wound base; superficial wound smears; and various types of swabs. Source: Adapted from Table 9, Clinical Study Report DUR001-303		

6.1.2.4.1 Baseline ABSSSI Pathogens (Micro-ITT population)

A total of 192 (91.4%) subjects in the dalbavancin single dose group and 196 (88.7%) subjects in the two-dose group had at least 1 gram-positive aerobic ABSSSI pathogen isolated at baseline either from a blood culture or culture from the primary ABSSSI site (**Table 9**).

Overall, *S. aureus* constituted about 65% of all isolates in both arms, and methicillin-resistant *S. aureus* accounted for about 16.7% (35/184) in single dose arm and 24.5% (54/174) in two-dose arm of all isolates. The prevalence of MRSA varied significantly by geographic region. In the US, 20.9% of subjects in the single-dose group (49.3% of the *S. aureus* isolates) and 31.9% in the two-dose group (59.3% of the *S. aureus* isolates) had MRSA whereas in Europe/South Africa, 1.0% of subjects in the single-dose group and 1.6% in the two-dose group had MRSA isolated from the baseline specimen.

Table 9 Baseline ABSSSI Pathogens (Micro ITT Population) : DUR001-303		
	Dalbavancin Treatment Group, n/N (%)	
	Single-Dose n=210	**Two-Dose n= 220**
Subjects with ≥ 1 gram- positive aerobe	192 (91.4)	196 (88.7)
Subjects with Staphylococcus aureus **	137 (65.2)	145 (65.9)
MRSA	35 (16.7)	54 (24.5)
MSSA	102 (48.6)	92 (41.8)
Streptococcus intermedius	16 (7.6)	11 (5.0)
Streptococcus pyogenes	14 (6.7)	22 (10.0)
Streptococcus constellatus	11 (5.2)	6 (2.7)
Streptococcus agalactiae	6 (2.9)	6 (2.7)
Streptococcus anginosus	6 (2.9)	2 (0.9)
		(b) (4)
Enterococcus faecalis	4 (1.9)	10 (4.5)
Streptococcus dysgalactiae	4 (1.9)	3 (1.4)
Streptococcus sanguinis	3 (1.4)	2 (0.9)
Subjects with≥ 1 gram-positive anaerobe	9 (4.3)	9 (4.1)
Clostridium perfringens	4 (1.9)	1 (0.5)
Peptoniphilus asaccharolyticus	0	4 (1.8)

Subjects with at least 1 gram-negative aerobe	17 (8.1)	27 (12.2)
Klebsiella pneumoniae	7 (3.3)	8 (3.6)
Enterobacter cloacae	1 (0.5)	4 (1.8)
Escherichia coli	1 (0.5)	3 (1.4)
Subjects with at least 1 gram-negative anaerobe	9 (4.3)	5 (2.3)
Prevotella bivia	3 (1.4)	1 (0.5)
** A subjects may have more than one *S. aureus* isolate; MRSA – methicillin-resistant *S. aureus*; MSSA – methicillin-sensitive *S. aureus*. Source: AXPATH analysis datasets for trials DUR001-303, and Clinical Study Report submission modules 5.3.5.1.		

Overall, about 44% of subjects had mono-microbial infection in single dose group and 46% in two-dose group in the ITT population. About 6% of patients in the ITT population had poly-microbial infections involving gram-negative pathogens. Of microITT population, about 73% of subjects had mono-microbial infection and 27% had poly-microbial infection at baseline in both groups.

Medical Reviewer's Comment: S. aureus was the most common baseline pathogen in both treatment groups. However, MRSA was isolated more frequently in the two-dose group (24.5% of all isolates in the mITT population) compared to the single dose group (16.7% of all isolates in the mITT population). Mono-microbial and poly-microbial isolates were similarly distributed between the two arms in both mITT and ITT population.

6.1.2.5 Non-drug Intervention

The proportions of patients who had non-drug interventions of any kind in the ITT population for ABSSSI prior to the first dose of study drug were similar across treatment groups. The most common non-drug intervention prior to the start of first dose of the study drug was incision and drainage (either operative or at bedside), which occurred for 4.3% of patients in both treatment groups. (**Table 10**)

Table 10 Most Common Non-drug Interventions Prior to Start of the Study Drug (ITT Population)		
	Dalbavancin Treatment Group, n (%)	
	Single-Dose N=349	**Two-Dose N=349**
Number of patients with at least one non-drug intervention prior to start of study drug	**33 (9.5%)**	**29 (8.3%)**
Incisional drainage	15 (4.3%)	15 (4.3%)
Wound treatment	14 (4.0%)	19 (5.4%)
Diagnostic aspiration	6 (1.7%)	4 (1.1%)
Abscess drainage	0	4 (1.1%)
Debridement	3 (0.9%)	0
Source: Clinical Study Report, Subject listing 16.2.10.1		

The most common non-drug intervention over the period from the first dose of study drug through day 3 after the first dose of study drug in ITT population was wound treatment

(40% in single dose; and 41% in two-dose group), followed by incision and drainage (25.8% and 24.6% of patients in single and two dose group respectively), and debridement (15.5% and 14.6% of patients in single and two dose group respectively). (**Table 11**)

Table 11 Non-drug Interventions by Time Period After the Start of Study Drug within 72 hours (ITT Population)		
	Dalbavancin Treatment Groups	
	Single-Dose N=349	**Two-Dose N=349**
Number of Patients with Any Non-drug Intervention <= 3 Days after the Start of Study Drug	**231 (66.2%)**	**231 (66.2%)**
Wound treatment	140 (40.1%)	143 (41.0%)
Incisional drainage	90 (25.8%)	86 (24.6%)
Debridement	54 (15.5%)	51 (14.6%)
Abscess drainage	27 (7.7%)	29 (8.3%)
Diagnostic aspiration	6 (1.7%)	9 (2.6%)
Wound drainage	8 (2.3%)	6 (1.7%)
Other *	21 (6.0%)	29 (8.3%)
Source: Clinical Study Report, Subject listing 16.2.10.1		

The rates of non-drug interventions were particularly explored for patients with cellulitis.

Most non-drug interventions occurred within first 3 days after starting study drug. It was noted that about 12% of patients with cellulitis in each group had incision and drainage and about 12% had debridement within first 3 days after the start of study drug (**Figure 6**). Proportions of patients with non-drug interventions that occurred through EOT were 14% and 12% for incision and drainage, 15% and 13% for debridement and 1.2% and 0.8% for abscess drainage in the two dose group and single dose groups respectively (**Figure 7**)

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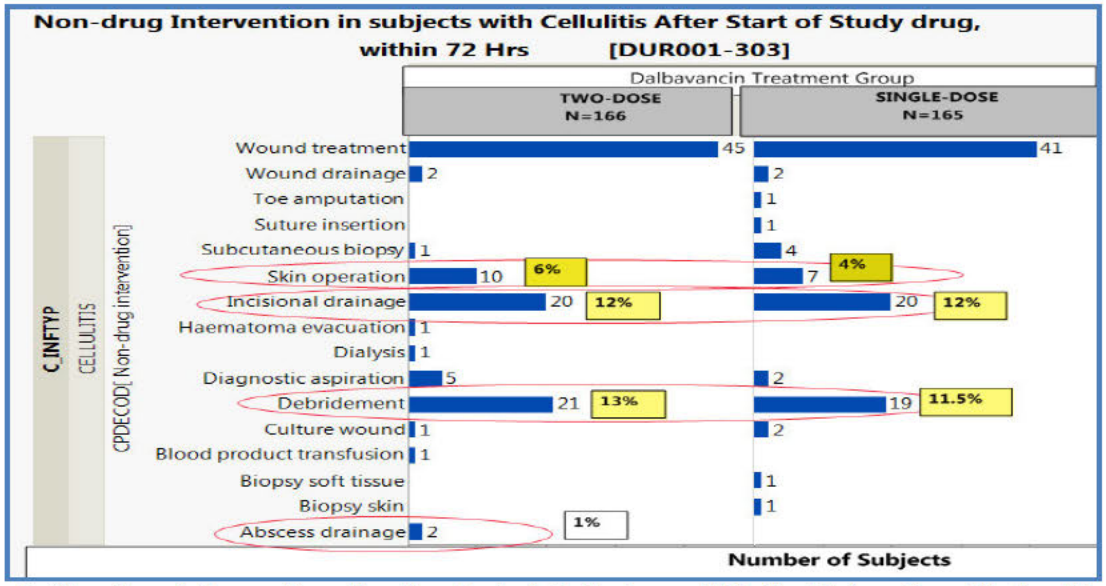

Figure 6 Non-drug Intervention after the start of study drug within first 3 days in subjects with Cellulitis; (Source: FDA Medical Reviewer analysis)

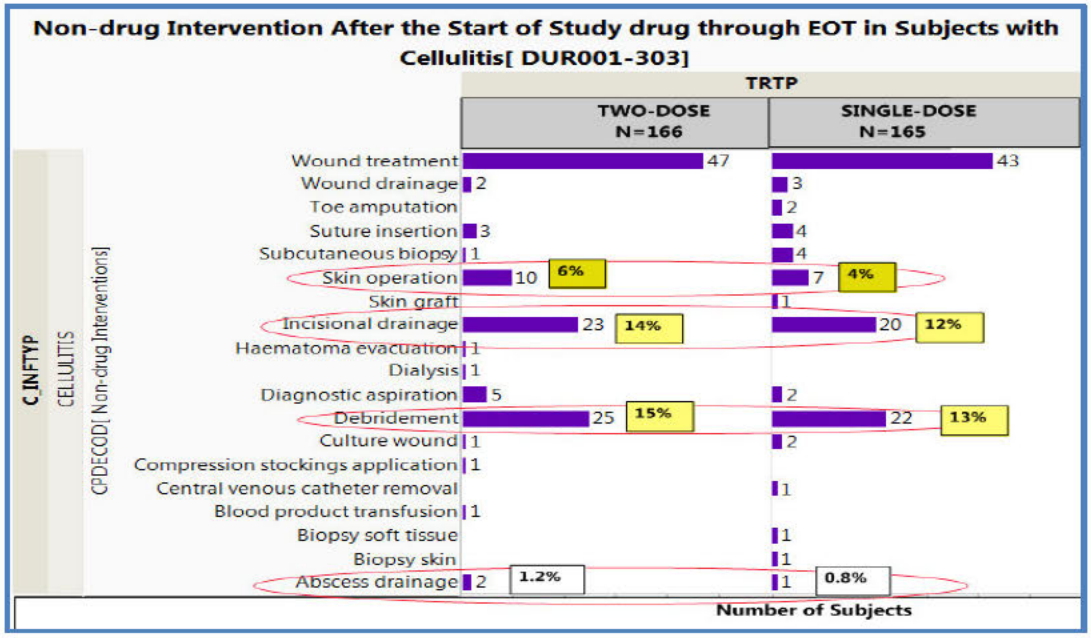

Figure 7 Non-drug Intervention after the start of study drug through EOT in subjects with Cellulitis; (Source: FDA Medical Reviewer analysis)

Table 12 describes the effect of non-drug therapies on early response and clinical success rates during assessment visits (Day 3-4, EOT and FV) in cellulitis patients. Patients in the single dose group performed worse compared to patients in the two doses group when non-drug therapies were received.

Table 12 Responder/Success Rates in Patients with Cellulitis Receiving vs. Not Receiving Non-drug Adjunctive Therapies (ITT Population)

Endpoint	Dalbavancin Single Dose (N=349) n (%)	Dalbavancin Two Dose (N=349) n (%)	Treatment Difference (95% CI)
Clinical Responder Rates at Day 3-4			
Received Non-Drug Therapies through Day 3-4	60/76 (79.0)	72/84 (85.7)	-6.8 (-19.2, 5.1)
Received no Non-Drug Therapies through Day 3-4	60/89 (67.4)	58/82 (70.7)	-3.3 (-17.0, 10.6)
Clinical Success Rates at EOT			
Received Non-Drug Therapies through EOT	65/79 (82.3)	78/87 (89.7)	-7.4 (-18.6, 3.3)
Received no Non-Drug Therapies through EOT	69/86 (80.2)	58/79 (73.4)	6.8 (-6.1, 19.8)
Clinical Success Rates at FV			
Received Non-Drug Therapies through FV	64/80 (80.0)	78/88 (88.6)	-8.6 (-20.1, 2.4)
Received no Non-Drug Therapies through FV	71/85 (83.5)	59/78 (75.6)	7.9 (-4.6, 20.5)

Source: FDA statistical reviewer

With regards to the use of antibacterial medication prior to the first dose of study , 22 subjects (6.3%) in the single-dose arm and 19 subjects (5.4%) in the two-dose arm received a systemic antibacterial agent in the 14 days prior to study drug assignment. The numbers of subjects who used any systemic antibacterial medication during the period from the first dose of study drug through the EOT visit were 39 subjects (11.2%) in the single-dose and 54 subjects (15.5%) in the two-dose group.

Medical Reviewer's Comment: The proportions of subjects with any kind of non-drug interventions for ABSSSI that were performed after starting study treatment, were similar across both groups. Additionally, the numbers of patients who used antibacterial medications either prior to the first dose or concomitantly with study drug were similar across treatment groups. The numbers of subjects who used any systemic antibacterial medication during the period from the first dose of study drug through the EOT visit were also similar across treatment groups. However, it was surprising to see a high number of debridement and incision and drainage procedures performed in subjects with infection type cellulitis. The reason for this is not clear.

Patients with cellulitis do not commonly require surgical procedures for the treatment of the index ABSSSI lesion. Importantly, surgical incision and drainage might influence treatment outcomes in patients with ABSSSI and confound efficacy analyses especially in trials with the primary efficacy outcome defined by a decrease in lesion size at 48-72 hours. This is why patients with abscesses, where surgical drainage is commonly needed were capped at no more than 30% of total patient enrollment.

The reviewer reviewed CRFs, wound assessment reports and images for the cases of cellulitis with these non-drug interventions to evaluate if these subjects may have had abscesses, and were incorrectly diagnosed with cellulitis. The review of available images gives the impression that cellulitis was diagnosed correctly. Additionally the proportion of subjects with cellulitis who underwent surgical procedures was similar in the US and non-US sites.

In addition, sensitivity analyses comparing clinical response in subjects with cellulitis who received surgical treatment versus those who were treated only with study drug were performed by the Biometrics reviewer in order to evaluate for possible confounding of efficacy outcomes by surgery. Overall, cellulitis patients who received non-drug therapies had lower clinical response and clinical success rates at Day3-4 and Final Visit respectively. In terms of treatment groups, patients in the single dose group performed worse compared to patients in the two doses group when non-drug therapies were received. The reader is referred to the statistical review for the details of these analyses.

6.1.2.6 Minimum Inhibitory Concentrations (MIC)

Applicant also provided MIC data on all gram-positive ABSSSI pathogens isolated at baseline from either the ABSSSI lesion or blood cultures. For each particular pathogen in the microITT population, dalbavancin MIC50, MIC90, and MIC ranges were 0.06 µg/mL, 0.06 µg/mL, and 0.015 to 0.12 µg/mL, respectively, for *S. aureus;* 0.001 µg/mL, 0.008 µg/mL, and 0.001 to 0.008 µg/mL, respectively, for *S. intermedius;* and 0.004 µg/mL, 0.015 µg/mL, and 0.004 to 0.03 µg/mL, respectively, for *S. pyogenes*. (**Table 13**)

Table 13 Minimum Inhibitory Concentration for Baseline Pathogens isolated from ABSSSI Site or Blood Culture (Micro-ITT Population)

	Dalbavancin Treatment Groups	
Pathogen (Gram Positives)	**Single Dose**	**Two-dose**
Staphylococcus aureus		
Number of Pathogens Isolated	144	162
Number of Pathogens with MIC Values	142	150
MIC 50 (ug/mL)	0.06	0.06
MIC 90 (ug/mL)	0.06	0.06
MIC Range (ug/mL)	0.03 - 0.12*	0.015 - 0.12*
MRSA		
Number of Pathogens Isolated	36	64
Number of Pathogens with MIC Values	35	56
MIC 50 (ug/mL)	0.06	0.06
MIC 90 (ug/mL)	0.06	0.06
MIC Range (ug/mL)	0.03-0.06	0.015 – 0.06
MSSA		
Number of Pathogens Isolated	108	98
Number of Pathogens with MIC Values	107	94
MIC 50 (ug/mL)	0.06	0.06
MIC 90 (ug/mL)	0.06	0.06
MIC Range (ug/mL)	0.03 - 0.12*	0.03 – 0.12*
Streptococcus intermedius		
Number of Pathogens Isolated	16	11
Number of Pathogens with MIC Values	14	9
MIC 50 (ug/mL)	0.001	-
MIC 90 (ug/mL)	0.008	-
MIC Range (ug/mL)	0.001 - 0.008	0.001 - 0.008
Streptococcus pyogenes		
Number of Pathogens Isolated	14	23
Number of Pathogens with MIC Values	14	22
MIC 50 (ug/mL)	0.004	0.004
MIC 90 (ug/mL)	0.015	0.015
MIC Range (ug/mL)	0.004 - 0.015	0.004 - 0.03
Streptococcus constellatus		
Number of Pathogens Isolated	11	6
Number of Pathogens with MIC Values	10	6
MIC 50 (ug/mL)	0.008	-
MIC 90 (ug/mL)	0.008	-
MIC Range (ug/mL)	0.004 - 0.03	0.004 - 0.03
Streptococcus agalactiae		

Number of Pathogens Isolated	6	6
Number of Pathogens with MIC Values	6	6
MIC 50 (ug/mL)	-	-
MIC 90 (ug/mL)	-	-
MIC Range (ug/mL)	0.008 - 0.015	0.008 - 0.015
Streptococcus anginosus		
Number of Pathogens Isolated	6	2
Number of Pathogens with MIC Values	6	2
MIC 50 (ug/mL)	-	-
MIC 90 (ug/mL)	-	-
MIC Range (ug/mL)	0.001 - 0.008	0.004 - 0.008
Enterococcus faecalis		
Number of Pathogens Isolated	4	10
Number of Pathogens with MIC Values	4	10
MIC 50 (ug/mL)	-	0.03
MIC 90 (ug/mL)	-	0.06
MIC Range (ug/mL)	0.03 - 0.06	0.03 - 0.06
Streptococcus dysgalactiae		
Number of Pathogens Isolated	4	3
Number of Pathogens with MIC Values	4	3
MIC 50 (ug/mL)	-	-
MIC 90 (ug/mL)	-	-
MIC Range (ug/mL)	0.008 - 0.008	0.008 - 0.008
Enterococcus faecium		
Number of Pathogens Isolated	2	1
Number of Pathogens with MIC Values	2	1
MIC 50 (ug/mL)	-	-
MIC 90 (ug/mL)	-	-
MIC Range (ug/mL)	0.03 - 0.12	0.06 - 0.06
Staphylococcus haemolyticus		
Number of Pathogens Isolated	2	1
Number of Pathogens with MIC Values	2	1
MIC 50 (ug/mL)	-	-
MIC 90 (ug/mL)	-	-
MIC Range (ug/mL)	0.03 - 0.03	0.06 - 0.06
Streptococcus anginosus group		
Number of Pathogens Isolated	0	1
Number of Pathogens with MIC Values	0	1
MIC 50 (ug/mL)	0	-
MIC 90 (ug/mL)	0	-
MIC Range (ug/mL)	0	0.04 - 0.004
* 2 MSSA isolates in single dose arm and 7 MSSA isolates in two-dose arm had MIC of 0.12; Source: Clinical study report, Table 14.1.18.1, DUR001-303		

For all pathogens in both the microITT and the respective ME populations, dalbavancin MICs were ≤0.06 µg/mL, with the following exceptions: 7 MSSA isolates in the two-dose group, 3 MSSA isolates in the single-dose group, and 1 *Enterococcus faecium* isolate in the single-dose group had MIC 0.12 µg/mL.

All gram-positive pathogens in the microITT population were susceptible to vancomycin (MIC of ≤1 µg/mL) except for two subjects (one in each group; (b) (6) in single dose and (b) (6) in two dose group), had *S. aureus* isolates with a vancomycin MIC of 2 µg/mL. Dalbavancin MIC for both of these subjects was 0.06, and both subjects had cellulitis as the type of infection. One subject was treated with a single dose of 1500mg of dalbavancin and was a non-responder at the 48-72 hour time-point, but had a clinical success at EOT and Final Visit. The other subject received the two-dose regimen of dalbavancin and was a clinical responder at the early time-point and clinical success at EOT and Final Visit.

6.1.2.7 Panton-Valentine leucocidin (PVL) Toxin

The Applicant also conducted the test for the presence of PVL toxin using a multiplex real time polymerase chain reaction (PCR) method for baseline *S. aureus* isolates. PVL was present in the 79 of 94, (84.0%) of MRSA isolates and 81 of 252, (32.1%) of MSSA isolates. All MRSA isolates were also positive for the presence of mecA gene.

6.1.3 Subject Disposition

In DUR001-303 trial, a total of 698 subjects were randomized, and were included in the ITT population with 349 subjects in the each treatment group. A total of 645 (92.4%) subjects completed the trial. The most common reason for withdrawal from the study in both groups was loss to follow-up, and the most common reason for study drug discontinuation in both groups were adverse events. Twenty-four patients (6.9%) in the single-dose group and 21 patients (6.0%) in the two-dose treatment group discontinued study drug, and 26 patients (7.4%) in the single-dose group were withdrawn from the study, versus 27 patients (7.7%) in the two-dose group. **Figure 8** illustrates disposition of subjects in trial DUR001-303. Details of disposition are discussed in section 7.3.3; Dropouts and/or Discontinuations.

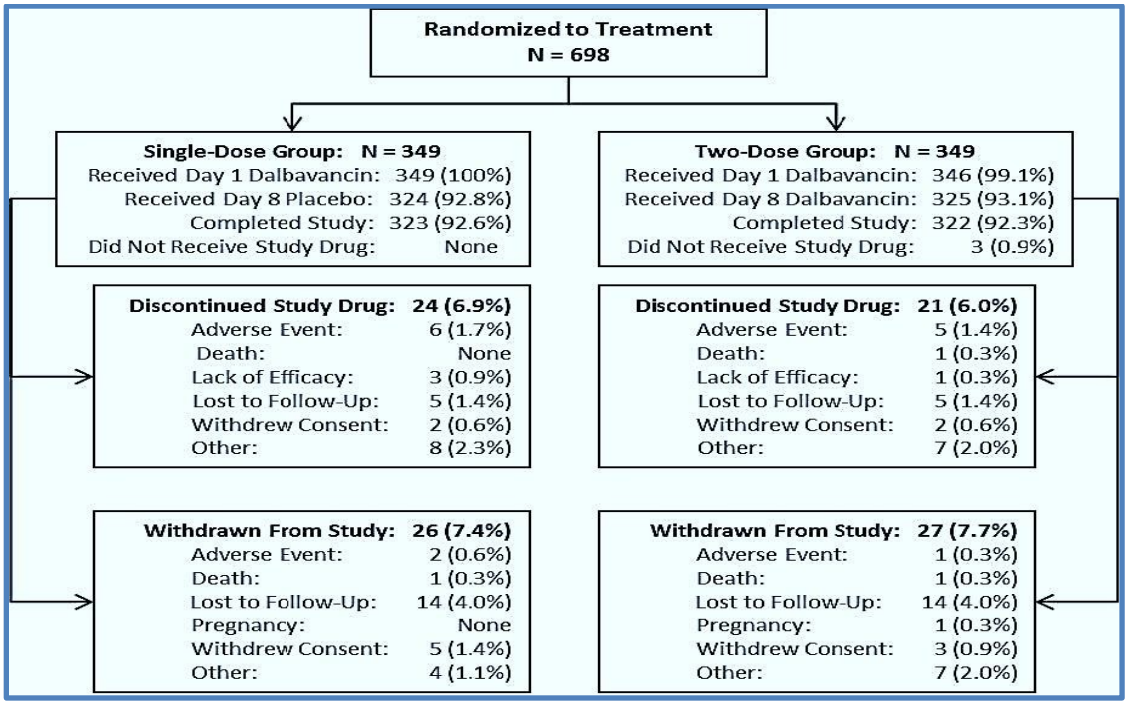

Figure 8 Subject Dispositions: Trial DUR001-303

Medical Reviewer's Comment: Overall patient disposition was fairly similar across treatment groups in the study. Three patients in the two dose group did not receive study drug due to technical issues at the investigational site; however, similar number of patients completed the study in both groups. The number of subjects who discontinued study drug due to adverse events was also similar in two groups.

6.1.4 Analysis of Primary Endpoint(s)

Primary efficacy endpoint was a clinical response defined as a decrease of ≥20% in lesion area (calculated as the longest length multiplied by the longest perpendicular width) at 48-72 hours post study drug initiation in a subject who was alive and had received no rescue therapy for ABSSSI. Patients who did not meet this definition were considered non-responders. Primary efficacy analyses were conducted in the ITT population.

6.1.4.1 Clinical Response at 48-72 hours

In trial DUR001-303, 93% of randomized patients in both treatment groups completed treatment with both doses of randomly assigned study drug (patients in the single dose group received placebo on day 8). A total of 284 (81.4%) subjects in the single dose arm and 294 (84.2%) in the two-dose arm were clinical responders at 48-72 hours (95% CI,-2.9; -8.5 to 2.8). (**Table 14**)

Table 14 Clinical response at 48– 72 hours : Trial DUR001-303			
Clinical Response at 48-72 hours	**Dalbavancin Single Dose**	**Dalbavancin Two Dose**	
ITT population	**N=349**	**N=349**	**Difference (95% CI)**
Clinical Responder	**284 (81.4%)**	**294 (84.2%)**	**-2.9 (-8.5, 2.8)**
Clinical Non-Responder	65 (18.6%)	55 (15.8%)	
Modified ITT population	**N = 349**	**N = 346**	
Clinical Responder	**284 (81.4%)**	**294 (85.0%)**	**-3.6 (-9.2, 2.0)**
Clinical Non-Responder	65 (18.6%)	52 (15.0%)	
Source: Clinical Study Report Table 13 and 14.2.2.1.1;			

Medical Reviewer's Comment: Both dalbavancin regimen groups performed similarly in primary efficacy response rates in ITT as well as mITT population. Applicant's results corroborated with FDA statistical analysis.

6.1.4.2 Clinical Response at 48-72 hours by ABSSSI Infection Type

Clinical response at 48-72 hours (also referred to as early clinical response) by ABSSSI infection type in the ITT population is presented in the **Table 15** below. There were relatively more responders with wound infection (93% in single dose arm and 89% in two-dose respectively), compared to patients with major abscess (85% and 89% in the single dose and the two dose group respectively), followed by cellulitis (73% and 79% in single and two dose group respectively) (**Figure 9**).

Table 15 Clinical Response at 48-72 Hours by Infection Type (ITT)		
	Dalbavancin Treatment Groups	
	Single Dose (N=349)	**Two-Dose (N=349)**
TRAUMATIC WOUND / SURGICAL SITE INFECTION		
Clinical Responder	89 /96 (93%)	82 /92 (89%)
Clinical Non-Responder	7 /96 (7%)	10 /92 (11%)
Difference (95% CI)	3.6 (-5.0, 12.6)	
MAJOR ABSCESS		
Clinical Responder	75 /88 (85%)	82 /91 (90%)
Clinical Non-Responder	13 /88 (15%)	9 /91 (10%)
Difference (95% CI	-4.9 (-15.1, 5.0)	
CELLULITIS		
Clinical Responder	120 /165 (73%)	130 /166 (78%)
Clinical Non-Responder	45 /165 (27%)	36 /166 (22%)
Difference (95% CI)	*-5.6 (-14.9, 3.7)*	
Source: Partially adapted from Clinical study reports, Table 14.2.2.1.5.0, DUR001-303		

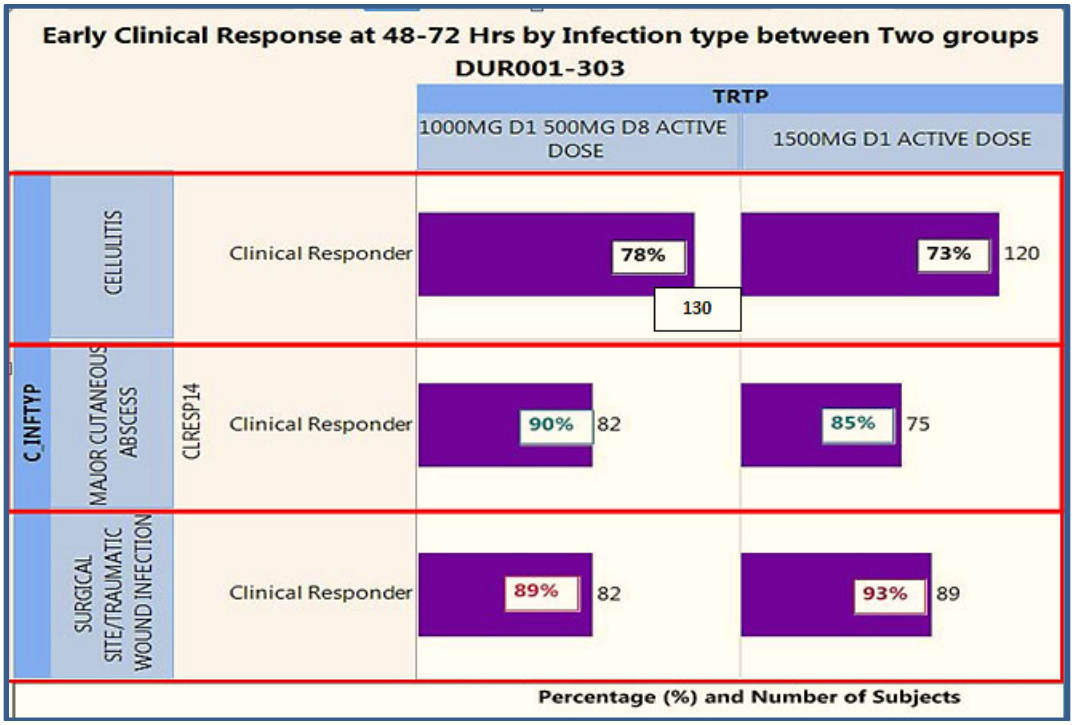

Figure 9 Clinical Response at 48-72 hours by infection type: trial DUR001-303
(Source: FDA Medical Reviewer analyses)

Medical Reviewer's Comment: Overall, in DUR001-303 trial, there were relatively more early clinical responders in patients with wound infection compared to the two other infection types in both treatment groups. It was noteworthy that early clinical response was lower in patients with cellulitis in both groups, despite having a high number of patients having additional non drug interventions (e.g. incision & drainage, and debridement procedures) after the study drug was started, which is unanticipated in cases of cellulitis. The finding of overall lower response rates could imply that non-surgical procedures may not have significantly impacted efficacy outcomes in patients with cellulitis.

The rate of early clinical response varied between two treatment groups based on the infection type. There were somewhat more early responders among patients with wound infection in the single dose as compared to the two dose group,93% vs. 89% respectively , whereas in patients with major abscess and cellulitis the response rates in the single dose group were lower as compared to the two dose group, 85% vs. 90% and 73% vs. 78% respectively. Overall, the response rates at 48-72 hours in patients with different infection types were balanced between the study groups.

6.1.4.3 Clinical Response at 48-72 hours by Geographic region and Infection Type

Early clinical response also varied by regions. In the US sites, patients with wound infection responded better to the single dose as compared to the two dose regimen, 92.2% vs 85.7%, respectively, whereas clinical response rate in patients with cellulitis was lower in the single dose as compared to the two dose group, 60.9% vs 76.1%, respectively. Response rate for major abscess was similar in the single and two dose groups, 88.5% vs 87.7% respectively.

Conversely in non-US sites, patients with major abscess responded better with the two dose regimen (77.8% vs 96.2% with the single and two dose regimen respectively), whereas, both regimens performed similarly in patients with cellulitis and wound infection (77.3% vs 79.2% and 93.3% vs 93.0% with single and two dose regimen respectively) (**Table 16**). Overall, the number of patients in the study arms when divided by an infection type and geographic region was small and the significance of these differences in the clinical response rate is uncertain.

Table 16 Clinical Response at 48-72 Hours by Geographic region and Infection Type (ITT Population)

	Dalbavancin Treatment Groups	
	Single Dose	**Two-Dose**
NORTH AMERICA		
MAJOR ABSCESS		
Clinical Responder	54 /61 (88.5%)	57 /65 (87.7%)
Clinical Non-Responder	7 /61 (11.5%)	8 /65 (12.3%)
Difference (95% CI)	*0.8 (-11.3, 12.8)*	
***TRAUMATIC WOUND / SURGICAL SITE* INFECTION**		
Clinical Responder	47 /51 (92.2%)	42 /49 (85.7%)
Clinical Non-Responder	4 /51 (7.8%)	7 /49 (14.3%)
Difference (95% CI)	*6.4 (-6.5, 20.1)*	
CELLULITIS		
Clinical Responder	28 /46 (60.9%)	35 /46 (76.1%)
Clinical Non-Responder	18 /46 (39.1%)	11 /46 (23.9%)
Difference (95% CI)	*-15.2 (-33.4, 3.9)*	
REST OF THE WORLD		
CELLULITIS		
Clinical Responder	92 /119 (77.3%)	95 /120 (79.2%)
Clinical Non-Responder	27 /119 (22.7%)	25 /120 (20.8%)
Difference (95% CI)	*-1.9 (-12.4, 8.7)*	
***TRAUMATIC WOUND / SURGICAL SITE* INFECTION**		
Clinical Responder	42 /45 (93.3%)	40 /43 (93.0%)

Clinical Non-Responder	3 /45 (6.7%)	3 /43 (7.0%)
Difference (95% CI)	*0.3 (-12.0, 13.0)*	
MAJOR ABSCESS		
Clinical Responder	21 /27 (77.8%)	25 /26 (96.2%)
Clinical Non-Responder	6 /27 (22.2%)	1 /26 (3.8%)
Difference (95% CI)	*-18.4 (-37.9, 0.0)*	
Source: Clinical Study Report, Module 5.3.5.1, Table 14.2.2.1.5.1		

6.1.4.4 Clinical Response at 48-72 hours by Presence or Absence of Fever

Clinical response rates at 48 to 72 hours by presence or absence of fever for trial DUR001-303 are presented in **Table 17.** Overall, clinical response rates were higher among subjects with fever at baseline (84% and 88% in the single and two dose groups respectively). Among afebrile subjects, response rate were similar in two arms (70% and 70% in both groups).

Table 17 Clinical Response at 48-72 Hours by Presence/Absence of Fever at Baseline (ITT Population)

	Dalbavancin Treatment Groups	
	Single Dose, N=349	**Two-Dose, N-349**
Fever at baseline	***n=290***	***n=283***
Clinical Responder	243 /290 (84%)	250 /283 (88%)
Clinical Non-Responder	47 /290 (16%)	33 /283 (12%)
Afebrile at Baseline	***n=59***	***n=66***
Clinical Responder	41 /59 (70%)	44 /66** (70%)
Clinical Non-Responder	18 /59 (31%)	22 /66** (33%)

** 3 subjects assigned to two dose arm were not treated and had no baseline temperature recorded, reviewer considered them as non-responders;

Source: FDA Medical Reviewer's AXEF dataset analysis

6.1.4.5 Time to >20% Reduction in Infection Area in ITT Population

Median time for >20% reduction in infection area was similar in both arms (65.3 hours and 65.6 hours in single dose and two dose groups respectively) in ITT population (**Figure 10).**

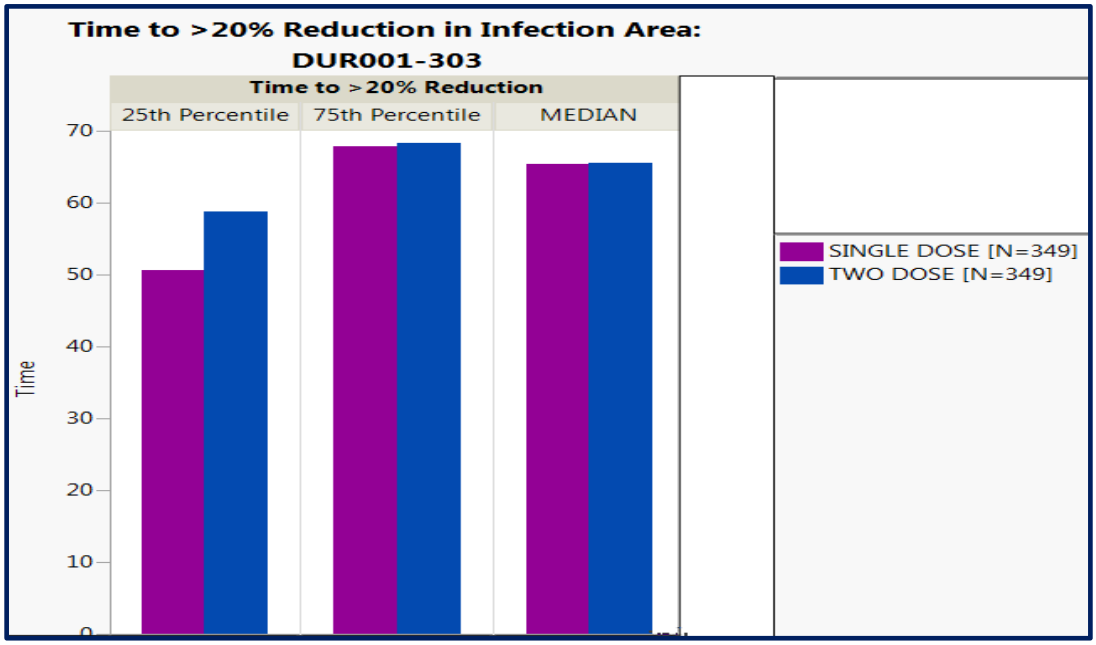

Figure 10 Time to 20% Reduction in Infection Area; ITT Population, trial DUR001-303
(Source: FDA Medical Reviewer analysis)

6.1.5 Analysis of Secondary Endpoints

The secondary endpoints were clinical status at EOT (day 14-15) in the ITT and CE populations, and clinical status at the Final Visit (28 ±2 days after initiation of study drug) in the ITT and CE populations.

Although no formal NI hypothesis testing was planned for either secondary efficacy analysis, for clinical status at the Final Visit the statistical analysis included a comparison in the ITT population with an expectation that in a one-sided comparison at the 2.5% level of significance, the lower limit of the 95% CI for the difference between treatment groups would be greater than -15%.

Among ITT population, clinical success at EOT was 84% and 84.8% and at Final Visit were 84.5% and 85.1% in single dose and two dose groups respectively. (**Table 18**, Figure **11**) For CE population, clinical success at EOT was 88.4% versus 89.4%, and at Final Visit was 92.3% versus 92.5% in single dose and two dose groups respectively. (**Table 18**)

Table 18 Secondary Clinical Efficacy Endpoint Analysis :Trial DUR001-303			
Endpoints	**Dalbavancin Treatment Groups**		
	Single Dose, n/N (%)	**Two Doses, n/N (%)**	**Difference,(95% CI)**
Clinical Success at EOT **(ITT)**	293/349 (84.0)	296/349 (84.8)	-0.9 (-6.3, 4.6)
Clinical Success at Final Visit **(ITT)**	295/349 (84.5)	297/349 (85.1)	-0.6 (-6.0, 4.8)
Clinical Success at EOT **(CE-EOT)**	267/302 (88.4)	270/302 (89.4)	-1.0 (-6.1, 4.1)
Clinical Success at Final Visit **(CE-FV)**	250/271 (92.3)	247/267 (92.5)	-0.3 (-4.9, 4.4)
Source: Analysis by FDA Statistical Reviewer			

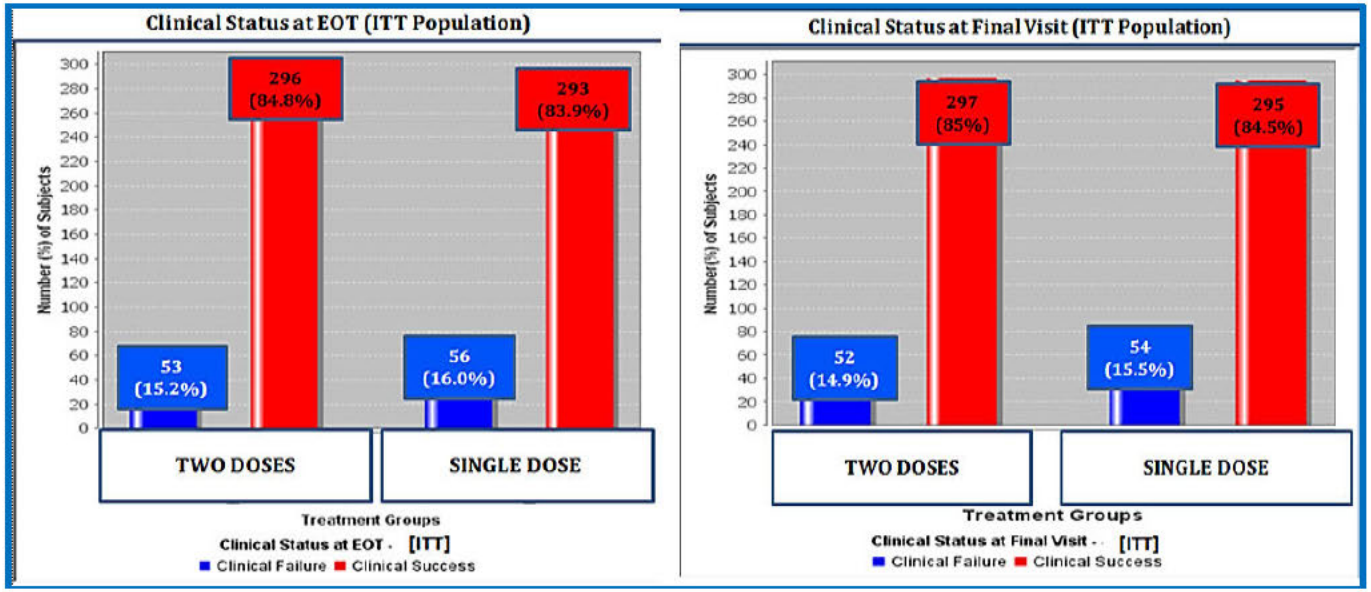

Figure 11 Clinical Status at EOT and FV in ITT Popultion
(Source : FDA Medical Reviewer's AXEF data Analysis)

Medical Reviewer's Comment: The clinical success rates were similar across treatment groups in both ITT and CE populations at EOT and Final Visits.

6.1.6 Subgroup Analysis

6.1.6.1 Concordance Analysis of Response Rates at 48-72 Hours and Clinical Status at EOT in the ITT Population

6.1.6.1a Clinical Status of Clinical Responders at 48-72 hours at EOT

The analyses of subjects who had clinical response at 48-72 hours were conducted to correlate with their clinical status at the EOT. In the ITT population there were 81.4% (284/349) and 84.2% (294/349) early responders in the single and two dose groups respectively. The proportion of subjects with both clinical success at 48-72 hours and at EOT was 73.4% (256/349) and 76.2% (266/349) in the single and two dose groups respectively and the proportion of subjects with clinical response at 48-72 hours but failure at EOT was 8% (28/349) in each treatment group. Clinical success rate at FV was 89.4% vs. 89.1%, for single dose and two dose groups respectively; and clinical failure rate was 10.6% and 10.9% for single dose and two dose groups respectively (**Table 19**)

Table 19 Clinical Status of Clinical Responders at 48-72 hours at the EOT and FV (ITT Population)

	Dalbavancin Treatment Groups	
	Single Dose N=349 n/ (%)	**Two Dose N=349** n/(%)
Early Responders	**284 (81.4)**	**294(84.2)**
Early Responders with Clinical Success at EOT	**256 (73.4)**	**266 (76.2)**
Early Responders with Clinical Failure at EOT	**28 (8)**	**28 (8)**
Early Responders with Clinical Success at FV	**254 (89.4)**	**262 (89.1)**
Early Responders with Clinical Failure at FV	**30 (10.6)**	**32 (10.9)**

EOT – end of treatment
Source: FDA Medical Reviewer's AXEF data analysis

Clinical success at EOT for subjects who were clinical responders at 48-72 hours was also analyzed by infection type. The proportion of subjects with both clinical success at 48-72 hours and at EOT in the single dose group was 66.8% (111/166), 72.5% (66/91) and 85.8% (79/92) for cellulitis, major abscess and wound infection respectively. In the two

dose group the proportion of these subjects was 70% (116/165), 84% (74/88), and 79% (76/96) for cellulitis, major abscess and wound infection respectively (**Figure 12**).

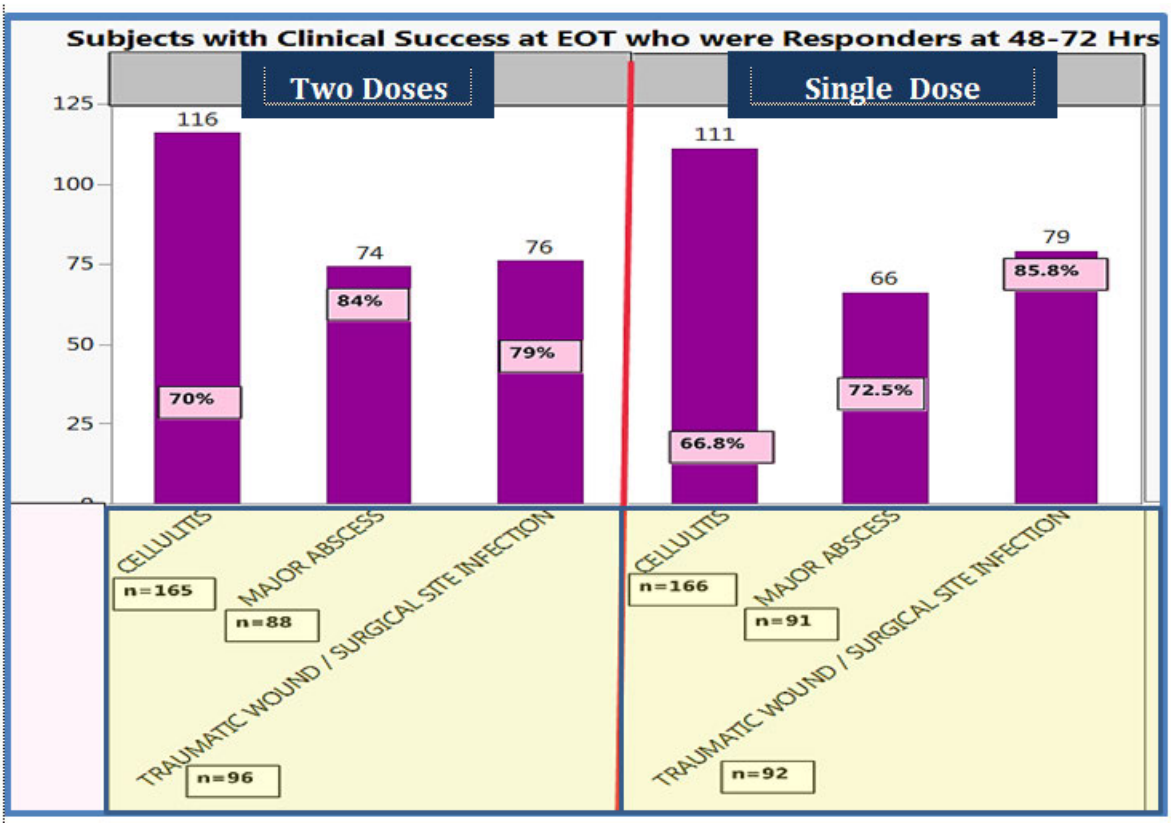

Figure 12 Clinical Success at EOT for subjects who were Clinical responders at 48-72 Hrs by Infection type ; (Source: FDA Medical Reviewer's AXEF data analysis)

Medical Reviewer's Comment: Considering the analysis by infection type, a slightly higher number of patients with wound infection in the single dose group were both clinical responders at 48-72 hours and clinical success at the EOT. Whereas in the two dose group, clinical success rate at EOT in these patients was slightly higher in patients with major abscess.

6.1.6.1b Clinical Status at EOT among subjects who were Non Responders at 48-72 hours

Clinical status at EOT for subjects who were non-responders at 48-72 hours was also examined. The proportion of early non-responders with clinical success at EOT was 37 (49.3%) and 30 (54.5%) and Final Visit was 41 (63.1%) and 35 (63.6%)in the single and two dose groups, respectively. Proportion of Early non responders who were clinical failure also at EOT were 28 (50.7%) and 25 (45.5%) in single and two dose groups respectively, and at Final Visit were 24 (36.9%) and 20 (36.4%) in single and two dose groups respectively. (**Table 20**)

Table 20 Clinical Status at the EOT and FV For subjects who were Non-Responders at 48-72 Hour (ITT)		
	Dalbavancin Treatment Groups	
	Single Dose, N=349 n/(%)	Two Dose, N=349 n/(%)
Early Non-responders	65 (18.6%)	55 (15.8%)
Early Non-responders With Clinical Success at EOT	37 (49.3)	30 (54.5)
Early Non-responders With Clinical Failure at EOT	28 (50.7)	25 (45.5)
Early Non-responders With Clinical Success at FV	41 (63.1)	35 (63.6)
Early Non-responders With Clinical Failure at FV	24 (36.9)	20 (36.4)
Source: FDA Medical Reviewer's AXEF data analysis		

Medical Reviewer's Comment: The outcome by concordance analysis between the primary and secondary endpoints was fairly balanced between single dose and two dose groups. Overall, it was reassuring to observe that clinical success rates among patients who were responders at 48-72 hours was much higher compared to non-responders at 48-72 hours, which provides the predictability of clinical success based on response at 48-72 hours.

6.1.6.2 Reason for Clinical Failure at EOT and Final Visit in ITT Population

The reasons for clinical failure in subjects who responded at 48-72 hours but had clinical failure at EOT and the Final Visit in the ITT population were further evaluated.
There were no notable differences between the treatment groups regarding the reasons for clinical failure. However, the reasons for clinical failure at the EOT and FV among all patients differed. For instance, early responders at FV failed more often due to missing data or receiving non-study systemic antibacterials while early responders at EOT failed more often due to lesion size not decreasing enough, local signs of infection or fever not resolving. (**Table 21**)

Table 21 Reason for Failure at EOT and Final Visit among Responders at 48-72 hours				
Responders at 48-72 hours	**Dalbavancin Single Dose n=284**	**Dalbavancin Two Doses n=294**	**Dalbavancin Single Dose n=284**	**Dalbavancin Two Doses n=294**
	At EOT Visit		**At Final Visit**	
Clinical Failures *	N=28	N=28	N=30	N=32
Indeterminates	N=8	N=11	N=18	N=21
No EOT/FV visit, missing all measurement data	8/8 (100%)	11/11 (100%)	17/18 (94.4)	18/21 (85.7%)
Have EOT/FV visit, but data are missing	0	0	1 /18 (5.6%)	3 /21 (14.3%)
Clinical Failures	N=20	N=17	N=12	N=11
Lesion size at EOT/FV did not decrease ≥ 80%/90% from Baseline	13/20 (65%)	11/17	6/12 (50%)	5/11 (45.5%)
Temperature at EOT/FV >37.6C	0	1/17 (5.9%)	0	0
Local signs of infection or fever have not resolved up to EOT/FV	17/20 (85%)	15/17 (88.2%)	5/12 (41.7%)	6/11 (54.5%)
Received non-study systemic antibacterial for ABSSSI up to EOT/FV	3/20 (15%)	1 (100%)	4/12 (33.3%)	5/11 (45.5%)
Death up to EOT/FV	1/20 (5%)	0	1/12 (8.3%)	0
***Clinical Failures & Indeterminates** Source: FDA Statistical Reviewer				

6.1.6.3 Efficacy Analyses by Key Target Pathogen at Baseline

6.1.6.3a Clinical Response at 48-72 hours by Key Target Pathogen at Baseline in micro-ITT Population

Early clinical response at 48-72 hours by key target pathogen in micro-ITT population is shown in **Table 22.** For *Staphylococcus aureus* isolates, success rates for MSSA were similar in both groups (89.3% vs 89.6% in single dose and two dose groups respectively). However for MRSA, success rate was little higher in single dose group (88.5% vs 78.7% in single dose and two dose groups respectively). For streptococcus species (relevant to ABSSSI), success rates were similar. There were 4 *Enterococcus faecalis* isolates in single dose group, all of which (100%) had early clinical response, and 10 *Enterococcus faecalis* isolates in two dose group, of which 8 (80%) showed early clinical response. (**Table 22**)

Table 22 Clinical Responders at 48-72 Hours by Key Target Pathogen at Baseline (MicroITT Population)				
	Dalbavancin Treatment Group, n/N (%)			
Key Target Pathogen at BL	**Single Dose**		**Two Dose**	
	n	**%**	**n**	**%**
Staphylococcus aureus	123/139	**(88.5)**	133/156	**(85.3)**
MRSA	31/36	**(86.1)**	48/61	**(78.7)**
MSSA	92/103	**(89.3)**	86/96	**(89.6)**
Streptococcus anginosus group	31/33	**(93.9)**	19/19	**(100.0)**
Streptococcus intermedius	**15/16**	(93.8)	11/11	(100.0)
Streptococcus pyogenes	**14/14**	(100.0)	18/22	**(81.8)**
Streptococcus constellatus	**10/11**	(90.9)	6/6	(100.0)
Streptococcus agalactiae	6/6	(100.0)	4/6	(66.7)
Streptococcus anginosus	6/6	(100.0)	2/2	(100.0)
Streptococcus dysgalactiae	4/4	(100.0)	3/3	(100.0)
Enterococcus faecalis	**4/4**	**(100.0)**	**8/10**	**(80.0)**
MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; Source of data: Clinical Study Report, Table 24				

6.1.6.3b Clinical Status at EOT visit in micro-ITT Population by Key Target Pathogen at Baseline

At the EOT Visit, response rate for key target pathogens was similar between the two groups in micro-ITT population. However, among *Staphylococcus aureus* isolates, response rate was slightly higher for MSSA in two dose compared to single dose group (89.3% with single dose and 94.8% with two dose regimen).

6.1.7 Subpopulations

In addition to Primary efficacy analysis by Infection type, geographic region, and key target pathogens presented above in section 6.1.4, Analysis of Primary End Points, Early clinical response was also evaluated in terms of age category ≥ 65 years and < 65 years. (**Table 23**) The proportion of clinical responders at 48-72 hours was slightly higher in the age category <65 years compared to ≥ 65 years in both treatment arms.

Table 23 Clinical Response at 48-72 hours by Age Category		
	Dalbavancin Treatment Groups	
Age category (years)	**Single Dose, n/N (%)**	**Two Doses, n/N (%)**
< 65	254/308 (82.5)	255/300 (85.0)
≥ 65	30/41 (73.2)	39/49 (79.6)
Source: FDA Reviewer analysis		

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The selection of the two-dose dalbavancin regimen already approved by FDA for the ABSSSI indication was based on PK and PD data from humans, animal models of infection, in vitro inhibitory and bactericidal activity, and a PK/PD analysis using population PK data and Monte Carlo simulation.

The approved two dose regimen was evaluated in a Phase 2 study in SSTI (VER001-5) comparing a single dose of dalbavancin 1100 mg (n=20) , a two dose of dalbavancin 1000 mg on day 1 and 500 mg on day 8 (n=21), and a comparator regimen (n=21). The primary efficacy endpoint was clinical response in the clinically evaluable population at 14 days after EOT. Clinical success rate was 61.5% in the dalbavancin single dose arm, 94.1% in the two dose arm, and 76.2% in the comparator arm. As a result, the two dose regimen was selected for subsequent registration trials. However, the utility of a single dose regimen was further explored to simplify the administration of dalbavancin.

The safety and PK profile of dalbavancin 1500 mg as a single dose has been examined in two studies (DUR001-101 and DUR001-102). The study DUR001-101 was a pilot trial of dalbavancin 1500 mg as a single dose in 8 healthy volunteers. Study DUR001-102 was a single-center, randomized, single-dose, placebo- and positive-controlled, parallel group ECG study to evaluate single IV doses of 1000 mg and 1500 mg dalbavancin. Fifty healthy volunteers were randomized into each of the 4 study groups. This study demonstrated that dalbavancin 1500 mg was well tolerated, with no significant effect on QT interval or other ECG parameters. The Cmax and AUC0-24 were each approximately 50% greater with the 1500 mg dose (**Table 24**). Results from Study DUR001-102 demonstrated that the increased plasma concentration observed for patients treated with the 1500 mg single dose was sustained throughout the first 24 hours after dosing (
Figure 13).

Table 24 Dalbavancin Pharmacokinetic Parameters at Increasing Doses Results from Study DUR001-102

Parameter	Dalbavancin Single 1000 mg	Dalbavancin Single 1500 mg
	N = 50	N = 49
AUC0-24h (mg·h/L)*	3184.82 (12.76)	4836.64 (13.71)
Cmax (mg/L)*	287.32 (13.92)	422.57 (13.21)
T_{max} (h)**	0.62 (0.62-0.68)	0.62 (0.62-1.12)

* Mean (%CV); ** Mean [Range]
Source: Clinical Study Report , DUR001-303, Table 1

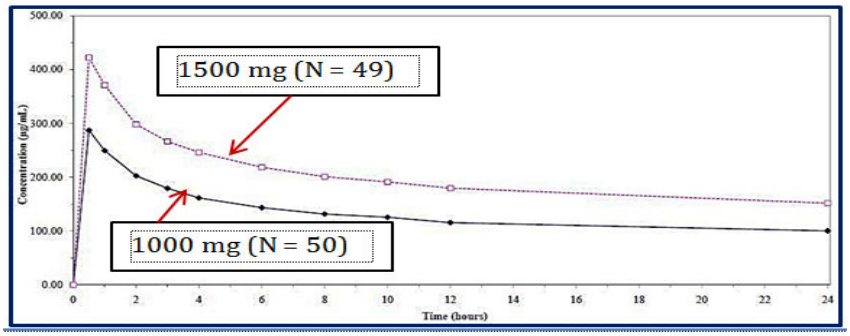

Figure 13 Mean Plasma Concentration for Dalbavancin: Results from Study 102

(Source: Adapted from Clinical Study Report, DUR001-303, Figure 3)

In addition, Applicant conducted a PK modeling to assess the PK/PD relationship for 3 different single doses (1000mg, 1500mg and 2000mg) over 120 hours across a range of MICs. The clinical outcome of interest was the probability of ≥20% reduction in lesion area. Five thousand simulated patients were included using simulated patient demographics, fixed and random effects parameter estimates for the population PK model, and Monte Carlo simulation techniques. This simulation supported the clinical presumption that a single dose of 1500 mg is comparable to the approved 2 dose regimen for most organisms with an MIC of ≥ 0.12 mcg/mL. Further detailed discussion on dose selection and PK is beyond the scope of this clinical review. Reader is referred to Clinical Pharmacology Review by Dr Yang for additional details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy analysis related to persistence of response is discussed in previous subsection of efficacy analysis.
There was no emergence of resistance observed so far in the phase 3 ABSSSI Studies (DUR001-301, DUR001-302 and DUR001-303), the cSSTI Pivotal Study (VER001-9), or the 3 supportive studies (VER001-16, VER001-8, and VER001-5).

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Clinical response at 48 to 72 hours and clinical status at the EOT in subjects with bacteremia at baseline in ITT population

The Applicant presented data on clearance of bacteremia at the EOT in subjects who had bacteremia at baseline. Number of patients with bacteremia at baseline in this study was low and similar between two groups. There were 12 out of 210 (5.7%) subjects in the single dose group and 10 out of 220 (4.5%) in the two dose group with bacteremia in micro- ITT population at baseline. Of those, 9 (4.3%) subjects in the single dose and 10 (4.5%) subjects in the two dose group had bacteremia with gram positive aerobic organisms.

The most frequently isolated pathogen from baseline blood cultures was *S. aureus*, and of those isolates, majority was MSSA. All of the patients in both treatment groups with gram-positive bacteremia at baseline and who had follow-up blood cultures for evaluation had clearance of bacteremia.

In Study DUR001-303, response rates for subjects with or without bacteremia were similar across two treatment groups. Ten of 12 patients (83.3%) with baseline bacteremia in the single dose group and 10 of 10 (100%) patients in the two dose group had early clinical response at 48-72 hours. By the EOT, 12/12 (100%) patients in single dose and 9/10 (90%) patients in two groups had clinical success.

Medical Reviewer's Comment: The number of subjects with bacteremia at baseline in two treatment groups was too low to draw any valid correlation between bacteremia and clinical outcomes.

6.1.11 Efficacy Conclusion

In trial DUR001-303 the Applicant has demonstrated that a single dose of dalbavancin 1500 mg is non-inferior to a two-dose regimen of dalbavancin (1000 mg on day 1 followed by 500 mg on day 8) for the treatment of ABSSSI based on clinical response at 48-72 hours.

Clinical success was sustained through Day 14-15 (EOT) and Day 28 (FV), and was similar between the two treatment groups. Success rates for clinical status at EOT and at FV for single dose versus two doses were 293/349 (84.0%) vs. 296/349 (84.8%), a difference of -0.9% (95% CI: -6.3, 4.6) and 293/349 (84.0%) vs. 296/349 (84.8%), a difference of -0.9% (95% CI: -6.3, 4.6), respectively.

When evaluated specifically by key target pathogens identified at baseline, clinical response was similar between the two treatment groups and there were no patients in either treatment group with a post-baseline gram-positive pathogen with decreased susceptibility to dalbavancin.

The results of this study, together with the findings of the pharmacokinetics and pharmacodynamics study, support the approval of a single dose of dalbavancin 1500 mg for the treatment of ABSSSI caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*), *and Enterococcus faecalis (vancomycin susceptible strains).*

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety evaluation for this review included data from a new trial DUR001-303 comparing the safety profile for the dalbavancin 1500 mg single-dose regimen versus the safety profile for the approved two-dose regimen. The evaluation of the safety of a single 1500 mg dose of dalbavancin was the primary objective of this review.

Applicant also submitted pooled safety data from all 8 completed Phase 2/3 dalbavancin clinical trials including trial DUR001-303. Pooled safety data from these trials were also analyzed to evaluate safety profile of all dosage regimens of dalbavancin as compared to comparators. Phase 2/3 trials from which safety data were pooled for analysis are summarized in **Table 25** below.

Table 25	**Phase 2 and Phase 3 Dalbavancin Trials (Safety Population)**				
Trial/ Phase	Design	Indication	Dalbavancin	Comparator	Dalbavancin Dose
VER001-4 (Phase 2)	Open-label	Catheter-related bloodstream infections with Gram-positive pathogens	40	34	*Grp A:* 1000 mg on day 1, 500 mg on Day 8. *Grp B:* 650 mg on day 1, 65 mg on days 2–14 (this arm was discontinued).
VER001-5 (Phase 2)	Open-label (1:1:1),	cSSTI	41	21	*Arm 1:* 1100 mg (single dose) on day 1 *Arm 2:* 1000 mg on day 1, 500 mg on day8
VER001-8 (Phase 3)	Double-blind (2:1)	uSSTI	367	186	1000 mg on day 1, with option to follow 500 mg on Day 8, possible switch to oral Placebo q6h.
VER001-9 (Phase 3)	Double-blind (2:1)	cSSTI	571	283	1000 mg on day 1, 500 mg on day 8, possible switch to oral placebo q12h
VER001-16 (Phase 3)	Open-label (2:1)	cSSTI or uSSTI	107	49	1000 mg on day 1, 500 mg on day 8.
DUR001-301 (Phase 3)	Double-blind (1:1)	**ABSSSI**	284	284	1000 mg on day 1, 500 mg on day 8

DUR001-302 (Phase 3)	Randomized (1:1), double-blind	**ABSSSI**	368	367	1000 mg on day 1, 500 mg on day 8
DUR001-303 (Phase 3)	**Randomized (1:1), double-blind**	**ABSSSI Single Dose**	**349**		1500 mg single dose
		Two-Dose	**346**		1000mg on day 1 and 500 mg day 8
Total			**2473**	**1224**	

The Safety population consisted of all subjects who received any amount of study drug (defined as dalbavancin, comparator, or placebo). For trials DUR001-301, -302 and -303, the safety population differs from ITT population. The latter was defined as all randomized subjects whether or not they received study drug. For the legacy trials the ITT population was defined as subjects who received at least one dose of study drug and therefore, was the same as the safety population.

7.1.2 Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after study drug administration, unless the event was captured in the study endpoint, as defined below. The event need not necessarily have a causal relationship with the treatment.
An event was to be considered as adequately captured in the study endpoint if it was accurately and fully represented by a protocol-defined reason for clinical failure (other than mortality) or relapse. Events represented by the study endpoints include all of the following, if related to the primary ABSSSI under study:

- Local signs of fluctuance and localized heat/warmth have not resolved;
- Local signs of tenderness to palpation and swelling/induration are worse than mild;
- For patients with a wound infection the severity of purulent drainage is worse than baseline;
- Persistence of one or more local or systemic signs and symptoms of ABSSSI such that new systemic antibacterial treatment was given;
- The patient had a temperature of > 37.6°C (by any measurement method) due to the ABSSSI;
- There is relapse/recurrence of ABSSSI (i.e., new or worsened signs or symptoms of the ABSSSI).

Adverse events were categorized and mapped to Preferred Terms (PTs) using the MedDRA Version 17.1. Treatment-emergent adverse events (TEAEs) include any adverse experience, whether or not it was considered study drug-related, which occurred during or after the onset of study drug administration. An event included any side effect, injury, toxicity,

sensitivity reaction, intercurrent illness, or sudden death. All AEs are organized by System Organ Class (SOC) and PT. Events that have the potential to be coded into several categories were checked manually as well as analyzed by creating Standardized MedDRA Queries (SMQs).

The intensity of each AE was graded as follows:

- Mild: Does not interfere with the patient's usual function.
- Moderate: Interferes to some extent with the patient's usual function.
- Severe: Interferes significantly with the patient's usual function.

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect;
- Is assessed as being a medically important event based on medical and scientific judgment. Such medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the above outcomes.

AEs of special interest in the Dalbavancin clinical development program include AEs associated with glycopeptides such as hypersensitivity reactions, local infusion-related reactions, nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia. In addition, drug-induced liver injury was considered an AE of special interest owing to cases of high-degree transaminase elevation which were observed at a higher rate in dalbavancin- as compared to comparator-treated in prior clinical trials.

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

Safety analyses are conducted separately for DUR001-303 trial and for pooled data from all 8 completed phase 2/3 studies including trial DUR001-303. Pooled data were analyzed in 4 treatment groups:

i. Dalbavancin Single-Dose Group: Included all 349 patients from Study DUR001-303 who received single dose of dalbavancin.
ii. Dalbavancin Two-Dose Group: Included 2124 patients from all 8 completed Phase 2/3 studies regardless of infection type and dosage regimens.
iii. Dalbavancin Any-Dose Group: Included all 2473 patients in completed Phase 2/3 studies who were treated with any dose of dalbavancin.
iv. Comparator Group: Included all 1224 patients in completed Phase 2/3 studies who were treated with active comparators, namely linezolid, cefazolin, cephalexin, or vancomycin.

It should be noted that although Applicant has integrated all phase 2/3 trials and presented as dalbavancin two dose regimen in two dose group, in VER001-4 patients were assigned dalbavancin dosage regimen of 650 mg on day 1 and 65 mg on days 2-14 and patients in trial VER001-5 received a single 1100 mg dose on day 1, with dalbavancin 500 mg dose on day 8 as optional for patients with uSSTI. In addition, 2 out of 7 phase 2 and 3 dalbavancin trials were open label. The trials were conducted for various indications and used different comparators. There were important differences in exclusion criteria and dosing regimens pertinent to safety assessments.

Table 26 Selected Differences in Study Population Selection Criteria between Phase 2/3 legacy Trials vs. DUR001-301, -302 and -303 ABSSSI Trials

	Prior Phase 2/3 trials (N=5)	DUR001-301, -302, and -303 (N=3)
CrCl ≤ 50 mL/min *	Excluded	Allowed
Oliguria **	Excluded from 3/5 trials	Allowed
Bilirubin > 2x the ULN	Excluded from all but VER001-5	Allowed

* ≤ 50 mL/min in VER001-5, VER001-8, and VER001-9; < 50 mL/min in VER001-4 and VER001-16; CrCl: creatinine Clearance
** Oliguria was defined as urine output < 20 cc/hour averaged over 24 hours; subjects with oliguria were excluded from VER001-4, VER001-8, and VER001-9 trials.
Source: NDA 21883 (clinical review, Dr Iarikov)

7.2 Adequacy of Safety Assessments

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

As mentioned above, the overall safety database submitted with this application includes 695 patients from trial DUR001-303 and pooled data from all completed Phase 2/3 trials which include a total of 3697 patients, including 2473 patients treated with any dose of dalbavancin (349 of which treated with 1500 mg single dose) and 1224 patients treated with comparator.

Exposure in Trial DUR001-303

In trial DUR001-303, in the single-dose group, all 349 patients (100%) in the ITT population received a day 1 dalbavancin dose. Four patients in this group received dalbavancin doses <1500 mg. In 3 patients, this was secondary to premature discontinuation of study drug due to an adverse event; the actual doses received by these 3 patients were 200, 305, and 315. For 1 patient, there was an error in calculating the CrCl which lead to the delivery of a reduced dose of 1000 mg.

In the two-dose group, 346/349 patients (99.1%) in the ITT population received a day 1 dalbavancin dose. Total of 326/349 patients (93.4%) received both the Day 1 and day 8 dalbavancin doses. Three patients were randomized to the two-dose regimen but never received the study drug. Additionally, there were 20 patients (5.7%) in this group who received the day 1 but not the day 8 dalbavancin dose.

All of the patients who had CrCl <30 mL/min without regular hemodialysis or peritoneal dialysis received appropriately reduced doses of dalbavancin (2 patients [0.6%] in the single-dose group and 7 patients [2.0%] in the two-dose group. (**Table 27**)

Table 27 Dalbavancin Exposure in Trial DUR001-303 (ITT Population)

	Dalbavancin Treatment Groups	
	Single Dose	**Two-dose**
Number of Patients with **Only One Dose** of Dalbavancin	349/349 (100.0%)	20+/349 (5.7%)
Number of Patients with **Two-dose** Dalbavancin: on day 1 and day 8	0	326/349 (93.4%)
Exposure based on CrCl		
Baseline CrCl < 30 mL/min without Dialysis, N1/N (%) +++	2/349 (0.6%)	7/349 (2.0%)
Dose Received on day 1, n/N1 (%)		
750	0	7/7 (100.0%)
1000	2/2 (100.0%)	0
Baseline CrCl >= 30 mL/min or on Dialysis, N1/N (%)	347/349 (99.4%)	340/349 (97.4%)
Dose Received on day 1, n/N1 (%)		
200	1*/347 (0.3%)	0
305	1*/347 (0.3%)	0
315	1*/347 (0.3%)	0
590	0	1/340 (0.3%)
900	0	1/340 (0.3%)
1000	1**/347 (0.3%)	337/340 (99.1%)
1500	343/347 (98.8%)	0

*Secondary to premature discontinuation of study drug due to an adverse event
** Error in calculating the CrCl which lead to a reduced dose of 1000 mg being delivered.
+ Received the day 1 but not the day 8 dalbavancin dose.
+++ All of the patients who had CrCl <30 mL/min without regular hemodialysis or peritoneal dialysis received appropriately reduced doses of dalbavancin: 2 patients (0.6%) in the single-dose group and 7 patients (2.0%) in the two-dose group.

Source: Data Adapted from ISS Module 5.3.5.3. Clinical study report, Table 14.2.1.2.2
Note: Numbers in denominator in two dose group changed to 349 (ITT population)by the reviewer (Applicant presented as 346)

Exposure in all completed phase2/3 trials

In all phase2/3 trials, 2473 patients received at least one dose of dalbavancin. A single dose of dalbavancin (1500 mg) was received by 349 patients, and 2124 patients received 2 doses of dalbavancin. Few patients discontinued study medication (which includes placebo treatment) because of an AE (2.5% of patients who received two-doses of dalbavancin and

1.7% of patients who received single dose dalbavancin). The majority of patients had ABSSSI (2010 overall, 1357 treated with dalbavancin). The integrated Phase 2/3 database also includes patient with CRBSI, SSSI, USSSI, cSSTI and cSSTI/uSSTI.
Table 28 below shows dalbavancin exposure by treatment group.

Table 28 Integrated Treatment Groups by Numbers of Patients exposed to Study Drug in All Phase 2/3 Studies

	Dalbavancin Dosage Regimen (N)				
Trial ID	**Single Dose, 1500 mg (N)**	**Two-Dose, 1000 mg on Day 1 and 500 mg on Day 8 (N)**	**Dalbavancin Any Dose (N)**	**Comparator (N)**	**Total (N)**
VER001-4 (CRBSI)	None	40*	40	34	74
VER001-5 (SSTI)	None	41*	41	21	62
VER001-8 (uSSTI)**	None	367	367	186	553
VER001-9 (cSSTI)	None	571	571	283	854
VER001-16 (cSSTI or uSSTI)	None	107	107	49	156
DUR001-301 (ABSSSI)	None	284	284	284	568
DUR001-302 (ABSSSI)	None	368	368	367	735
DUR001-303 €(ABSSSI)	349	346	695	None	695
Totals	**349**	**2124**	**2473**	**1224**	**3697**

CRBSI = Catheter-related bloodstream infections; SSTI = Skin and soft tissue infections; uSSTI = Uncomplicated SSTI; cSSTI = Complicated SSTI; ABSSSI = Acute bacterial skin and skin structure infections.
* Including 7 patients in VER001-4 for whom the assigned dalbavancin dosage regimen was 650 mg on day 1 and 65 mg on days 2-14 and 20 patients in Study VER001-5 for whom the assigned dalbavancin dosage regimen was a single 1100 mg dose on day 1.
** The dalbavancin 500 mg dose on day 8 was optional for patients with uSSSI in these trials.
€ Proposed trial of Single dose,1500 mg
(Adapted from Integrated Safety Summary Module 5.3.5.3)

Demographics of the Dalbavancin Phase 2/3 trial pool are discussed in section 6.1.2 of the efficacy review. Disposition of the safety population is discussed in section 7.3.3 of the safety review.

Medical Reviewer's Comment: The adequacy of safety data, and the extent and duration of exposure appears to be adequate to assess the safety of dalbavancin 1500 mg dose.

7.2.2 Explorations for Dose Response

The dose response of dalbavancin has been examined in phase 1 trials (VER001-1, VER001-2, DUR001-102, and DUR001-103). The PK of dalbavancin after multiple dosing has been examined in 3 phase 1 trials. The results of the trial indicated that there was no apparent accumulation after day 8 when subjects received 1000 mg on day 1 followed by weekly doses of 500 mg. The exposures (AUC 0-14 days) from the single-dose regimen (1500-mg) and two-dose regimen (1000-mg and day 1 and 500-mg on day 8) were comparable based on results from population PK analysis. Applicant has not observed any dose-limiting

toxicity with dalbavancin. Six subjects each cumulatively received total dalbavancin exposures of 4500 mg (3.0-fold the proposed exposure), 3500 mg (2.3-fold the proposed exposure), and 2500 mg (1.7-fold the proposed exposure) in Study DUR001- 104. Multiple doses of dalbavancin at total exposures of up to 4500 mg administered to healthy subjects were well tolerated.

Medical Reviewer's Comment: A dose dependent increase in incidence of AE was not seen in the dalbavancin trials including DUR001-303, which is a comparison between a single dose of 1500 mg with two doses of 1000 mg on day 1 followed by 500 mg on day (b) (4)

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was adequate. The reader is referred to section 4.3 Nonclinical Pharmacology/Toxicology of this review for more detail.

7.2.4 Routine Clinical Testing

In trial DUR001-303, study procedures were conducted at baseline and at a series of 6 time points thereafter. Treatment was started on day 1; baseline assessments were performed within 24 hours before the first dose of study drug, and patients were administered the first dose of study drug within 4 hours of randomization. On day 2, patients being treated on an outpatient basis were contacted by the investigator to check for worsening of the presenting ABSSSI lesion.

Efficacy assessments were performed on day 3-4, on Day 8 when patients were also administered the second dose of study drug, on day 14-15, which was defined as the EOT visit, and on day 28, which was defined as the Final Visit. Safety assessments were performed at every visit.

All patients who discontinued study treatment for any reason were encouraged to complete the trial, and at minimum had a final study visit within 3 calendar days after discontinuation, at which all EOT Visit procedures were performed. Such patients were also requested by the investigator to return for a Final Visit on day 28. The investigators were required to follow up with the patient through day 28 regarding any unresolved adverse events whether or not this Final Visit occurred.
Discussion of the trial is described in more detail in section 5.3, Discussion of individual Clinical Trials of this review.

Medical Reviewer's Comment: Routine clinical assessments in DUR001-303 trial were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

A total of 14 phase 1 clinical trials have been conducted to evaluate dalbavancin pharmacokinetics (PK) in healthy subjects and in subjects with renal and hepatic impairment. Since in vitro and in vivo studies suggested that dalbavancin is not a substrate, inducer, or inhibitor of hepatic cytochrome P450 (CYP) isozymes, no clinical drug-drug interaction studies have been conducted formally.
Drug-drug interactions were evaluated by evaluating AE profiles in subjects in phase 2 and 3 trials who received concomitant medications of special interest. Medications that were administered while patients were on dalbavancin therapy were grouped as cytochrome P450 substrates, inducers, or inhibitors. These medications included acetaminophen, aztreonam, fentanyl, metronidazole, furosemide, proton pump inhibitors, midazolam and simvastatin. The presence of cytochrome P450 substrates, inhibitors, inducers, or any of the individual concomitant medications had no significant effect on the clearance of dalbavancin. Drug-laboratory test interactions have not been reported with dalbavancin. Dalbavancin at therapeutic levels does not artificially prolong prothrombin time (PT) or activated partial thromboplastin time (aPTT). Details of coagulation study result are discussed in section 7.4.5, Special Safety Studies/Clinical Trials.

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

As a glycopeptide, dalbavancin may be associated with infusion-related reactions, nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia.
The potential for ototoxicity was evaluated with audiometric testing in a total of 105 subjects in six phase 1 trials. Initially audiometric testing was undertaken in study VER001-1 where abnormal audiograms were recorded for 5 subjects treated with dalbavancin and 2 treated with placebo. Subsequently, audiometric testing was performed in studies VER001-2, VER001-3, VER001-10, VER001-12, and VER001-13. The Applicant reported that the data were reviewed by a single central reviewer who concluded that there was no evidence of ototoxicity associated with dalbavancin. Hence, audiometric testing was not included in subsequent clinical trials.
As to other potential AEs associated with glycopeptides, routine clinical evaluations and laboratory testing conducted in the dalbavancin development program allowed their adequate assessment. The results of these analyses are presented in sections 7.4.1, Common Adverse Events and 7.4.2, Laboratory Findings.

7.3 Major Safety Results

The overall incidence of TEAEs, SAEs, discontinuation of study drug due to TEAEs, and deaths in DUR001-303 trial is summarized in **Table 29**.

Table 29 Overview of TEAEs in DUR001-303 and Pooled Phase2/3 Trials (Safety Population)				
	Trial DUR001-303		Pooled data All Phase2/3 trials	
	Dalbavancin Single Dose	Dalbavancin Two-Dose	Dalbavancin Any Dose	Comparator
	N=349	N=346	N=2473	N=1224
Number of patients who experienced at least one event	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any TEAE	70 (20.1)	69 (19.9)	938 (37.9)	573 (46.8)
TEAE by Intensity				
Mild	43 (12.3)	38 (11.0)	499 (20.2)	273 (22.3)
Moderate	19 (5.4)	24 (6.9)	326 (13.2)	239 (19.5)
Severe	8 (2.3)	7 (2.0)	113 (4.6)	61 (5.0)
TEAE Related to Study Drug	25 (7.2)	26 (7.5)	379 (15.3)	246 (20.1)
TEAE Leading to Premature Discontinuation of Study Drug	6 (1.7)	5 (1.4)	64 (2.6)	35 (2.9)
Withdrawal from study due to TEAE	3 (0.9)	1 (0.3)	22 (0.9)	6 (0.5)
Serious TEAE	7 (2.0)	5 (1.4)	121 (4.9)	80 (6.5)
Related to Study Drug	0	2 (0.6)	5 (0.2)	9 (0.7)
Deaths	1 (0.3)	1 (0.3)	12 (0.5)	14 (1.1)
Source: Partially adapted from ISS Module 5.3.5.3. modified by FDA Medical Reviewer				

Medical Reviewer's Comment: Analysis of pooled results from phase 2/3 trials shows overall similar incidence of TEAES in the dalbavancin and comparator arm with somewhat higher incidences of TEAE, moderate TEAEs, TEAEs related to study drug and SAEs in the comparator arm. The incidence of TEAEs in the single dose and two-dose dalbavancin groups in trial DUR001-303 were similar.

7.3.1 Deaths

There were no deaths among subjects who received dalbavancin in Phase 1 trials. All deaths occurred during the phase 2/3 development trials.

Overall, in prior phase 2/3 trials, there were slightly fewer deaths in dalbavancin as opposed to comparator treated patients. No deaths were attributed to be related to the study drugs. A total of 26 deaths occurred in dalbavancin trials. Among those, 24 deaths occurred in prior dalbavancin trials (10 [0.005%] in dalbavancin group and 14 [1.1%] in the comparator group), and 2 deaths occurred during trial DUR001-303, one in each arm. (**Table 30**)

Table 30 Deaths that Occurred During Dalbavancin Development Program

Prior Phase 2 and 3 Trials *		DUR001-303		All Phase 2 and 3 trials	
Dalbavancin (2 doses) (N=2124)	Comparator (N=1224)	Dalbavancin (single dose) (N=349)	Dalbavancin (2 doses) (N=346)	Dalbavancin (N=2473)	Comparator (N=1224)
10 (0.5%)	14¥ (1.1%)	1 (0.002%)	1 (0.002%)	12 (0.5%)	14¥ (1.1%)
				Total : 12	**Total : 14**

* VER001-4, VER001- 5, VER001-8, VER001-9, VER001-16, DUR001-301, and DUR001-302;
¥ In trial 302, Subject (b) (6) from the comparator arm died after being withdrawn from the trial. The reason for withdrawal was an infection with gram-negative pathogens.

For patients who received any dose of dalbavancin in Phase 2/3 studies (N=2473), cardiopulmonary failure resulted in an outcome of death for 2 (0.1%) patients, and cardiac arrest, cardiac death, cardiac failure congestive, cardiogenic shock, myocardial infarction, pulmonary embolism, pulmonary edema, respiratory failure, sepsis, toxicity to various agents and tracheal hemorrhage having an outcome of death for 1 (0.04%) patient each. There was one death due to toxicity due to various agents (heroin and methamphetamine) in the group of patients who received only a single dose of dalbavancin in trial DUR001-303. (**Table 31**)

For patients who received the comparator (N=1224), cardiopulmonary failure and cardiovascular accident had an outcome of death for 2 (0.2%) patients, and cardiac arrest, cardiac failure congestive, pulmonary edema, acute coronary syndrome, cardiac failure acute, chronic obstructive pulmonary disease, hypovolemia, metastatic gastric cancer and sudden death having an outcome of death for 1 (0.1%) patient each (**Table 31**).
All the deaths in prior dalbavancin phase 2/3 trials were also considered unrelated to study drugs. (**Table 31**)

Table 31 Deaths in Dalbavancin Phase2/3 Trials						
Treatment Arm	**Age**	**Patient ID**	**Preferred Term**	**Start/Stop Day**	**Study Day**	**Relationship to Study Drug ***
Dalbavancin 1 dose	47	(b) (6)	Toxicity to various agents	11 / 12	12	Unrelated
Dalbavancin 2 doses	59		Pulmonary embolism	4/4	4	Unrelated
			Pulmonary edema	4/4		
	78		Sepsis	26/32	32	Unrelated
	74		Cardiac failure congestive	7/10	10	Unrelated
	75		Respiratory failure	22/22	22	Unrelated
	55		Respiratory failure	21/21	21	Unrelated
	68		Tracheal hemorrhage	17/17	17	Unrelated
	67		Cardiogenic shock	5/5	5	Unlikely related
	84		Cardiac arrest	21/21	21	Unrelated
	82		Cardiopulmonary failure	9/23	23	Unrelated
	59		Cardiac death	4/4	4	Unrelated
	55		Myocardial infarction	9/10	10	Unlikely related
Comparator	73		Cardiac failure congestive	31/32	32	Unrelated
	62		Systemic lupus erythematosus	41/49	49	Unrelated
	79		Cardiac failure acute	4/4	4	Unrelated
	69		Pulmonary embolism	5/5	5	Unrelated
	68		Cardiopulmonary failure	52/52	52	Unrelated
			Hypovolemia	29/52		
	57		Sudden death	39/39	39	Unrelated
	78		Cardiopulmonary failure	41/41	41	Unrelated
	65		Cerebrovascular accident	6/9	9	Unrelated
	64		Metastatic gastric cancer	12/12	12	Unrelated
	76		COPD	14/21	21	Unrelated
	72		Acute coronary syndrome	43/55	55	Unlikely related
	67		Cardiac arrest	12/12	12	Unrelated
	47		Cerebrovascular accident	8/12	12	Unrelated
	82		Pulmonary edema	23/48	48	Unrelated

* Investigator assessment ; COPD: Chronic Obstructive Pulmonary Disease

7.3.1.1 Narratives of Deaths from Trial DUR001-303

Trial 303, Subject ID (b) (6) (Single dose dalbavancin group)

The patient was a 47-year-old white male who presented with cellulitis of the left lower arm. His baseline cultures were negative. He had a medical history of bipolar disorder, schizophrenia, hepatitis C, ongoing IV drug abuse with heroin and occasional methamphetamine, tobacco use, anxiety, and an unspecified sleep disorder. On day 1 and day 8 the patient received study medication per protocol (dalbavancin 1500 mg IV on day 1 and placebo infusion on day 8). On day 14 the patient's acquaintance arrived at the study site and reported that he had committed suicide on day 12. The next day, autopsy revealed that the cause of death was a result of combined heroin and methamphetamine intoxication. The patient was also found to have cardiomegaly with two-vessel severe coronary artery atherosclerosis. Investigators considered the death unrelated to study drug.

Trial 303, Subject ID (b) (6) (Two-dose dalbavancin group)

The patient was a 59-year-old white female, who presented with cellulitis of the right lower leg. Her baseline cultures were negative. The patient's medical history included hypertension, hypertensive heart disease, heart failure and overweight (BMI 28.9). Baseline medications were nebivolol, lisinopril dihydrate/amlodipine besylate, clopidogrel, omeprazole and ketoprofen intramuscular. On day 4, while still hospitalized, she lost consciousness and had cardiopulmonary arrest. Autopsy report listed the cause of death as thromboembolism of the main pulmonary artery, thrombosis of deep veins of lower extremities (including right tibia near cellulitis) and ischemic heart disease (diffuse cardio sclerosis due to obliterating atherosclerosis of coronary artery). Risk factors for thrombosis included hypertension, heart failure, and being overweight; it is unknown if patient had other risk factors (such as smoking, malignancy, or immobility). Investigators considered the death unrelated to study drug.

Medical Reviewer's Comment: After reviewing the details of the clinical course of the above patients by exploring the CRFs and data available, this reviewer agrees with the investigator's assessment. Both patients' demise appears to be primarily a consequence of intoxication in case of death in the single dose group, and thromboembolism secondary to underlying medical conditions in the two-dose group rather than be related to the study medication.

7.3.2 Nonfatal Serious Adverse Events

The incidence of serious adverse events (SAEs) in the trial DUR001-303 was low and similar across the treatment groups. Seven patients (2.0%) in the single-dose group and 5 patients (1.4%) in the two-dose group had SAE. (**Table 32**)

Table 32 Serious Treatment Emergent Adverse Events in Trial DUR001-303 by SOC and PT (Safety Population)				
			Dalbavancin Treatment Group, n (%)	
	Start of AE[π]	End of AE[π]	Single-Dose (N = 349)	Two-Dose (N = 346)
Number of events			**10**	**5**
Subjects with at least 1 event			***7 (2.0)***	***5 (1.4)***
SOC, Eye disorders			**1 (0.3)**	**0**
Vitreous hemorrhage	12	20	**1 (0.3)**	**0**
SOC, Infections and infestations			**4 (1.1)**	**2 (0.6)**
Clostridium difficile colitis*	16	35	**0**	**1 (0.3)**
Necrotizing fasciitis**	4	20	**0**	**1 (0.3)**
Pneumonia	16	20	**1 (0.3)**	**0**
Sepsis**	5	8	**1 (0.3)**	**0**
Skin bacterial infection**	3	5	**2 (0.6)**	**0**
SOC, Injury, poisoning, and procedural complications			**1 (0.3)**	**0**
Toxicity to various agents***	11	12	**1 (0.3)**	**0**
SOC, Metabolism and nutrition disorders			**1 (0.3)**	**0**
Hyperglycemia**	4	6	**1 (0.3)**	**0**
SOC, Renal and urinary disorders			**0**	**1 (0.3)**
Acute renal failure	3	30	**0**	**1(0.3)**
SOC, Respiratory, thoracic, and mediastinal disorders			**0**	**1 (0.3)**
Pulmonary embolism***	4	4	**0**	**1(0.3)**
SOC, Skin and subcutaneous tissue disorders			**0**	**1 (0.3)**
Urticaria*	9	17	**0**	**1(0.3)**
SOC, Vascular disorders			**2 (0.6)**	**0**
Deep vein thrombosis	9	53	**1 (0.3)**	**0**
Peripheral ischemia	7	24	**1 (0.3)**	**0**
Phlebitis	9	20	**1 (0.3)**	**0**

* Related to study drug (Investigator's assessment);
** Lead to discontinuation of study drug (one of the two skin bacterial infection cases lead to discontinuation of the study drug);
*** Resulted in death
π Start and End day are study days.
SOC: System Organ Class; PT: Preferred Term

Medical Reviewer's Comment: Two of the SAEs (Clostridium difficile colitis and Urticaria) were assessed by the investigator as being related to the study drug. Medical reviewer concurs with the assessment after review of case report forms. Narratives of SAEs, considered related to the study drug are described below.

In the pooled phase 2/3 trials SAEs were reported for 7 patients (2.0%) who received a single dose of dalbavancin, 114 patients (5.4%) who received 2 doses of dalbavancin, 121 (4.9%) patients who received any dose of dalbavancin, and 80 patients (6.5%) who received the control comparator drug. Overall, the rates of SAEs were similar in dalbavancin and comparator-treated patients. Cellulitis was the most common serious TEAE but its incidence was similar in the dalbavancin and comparator arm, 15(0.6%) and 7(0.6%) respectively. (**Table 33**)

Table 33 Serious Adverse Events : Pooled Data from 8 Phase 2/3 Dalbavancin Trials

	Dalbavancin Dosage Regimen			Comparator
	Single Dose	Two-Dose	Any Dose Any Regimen	Comparator
Event*, n (%)	**N = 349**	**N = 2124**	**N = 2473**	**N = 1224**
At least one SAE	**7 (2.0)**	**114 (5.4)**	**121 (4.9)**	**80 (6.5)**
Cellulitis	0	15 (0.7)	15 (0.6)	7 (0.6)
Cardiac failure congestive	0	4 (0.2)	4 (0.2)	2 (0.2)
Abscess limb	0	3 (0.1)	3 (0.1)	1 (0.1)
Asthma	0	3 (0.1)	3 (0.1)	0
Atrial fibrillation	0	3 (0.1)	3 (0.1)	1 (0.1)
Deep vein thrombosis	1 (0.3)	2 (0.1)	3 (0.1)	2 (0.2)
Necrotizing fasciitis	0	3 (0.1)	3 (0.1)	1 (0.1)
Osteomyelitis	0	3 (0.1)	3 (0.1)	3 (0.2)
Peripheral ischemia	1 (0.3)	2 (0.1)	3 (0.1)	0
Pneumonia	1 (0.3)	2 (0.1)	3 (0.1)	2 (0.2)
Accidental overdose	0	2 (0.1)	2 (0.1)	1 (0.1)
Anal abscess	0	2 (0.1)	2 (0.1)	1 (0.1)
Arthritis bacterial	0	2 (0.1)	2 (0.1)	0
Bacteremia	0	2 (0.1)	2 (0.1)	1 (0.1)
Cardio-respiratory arrest	0	2 (0.1)	2 (0.1)	0
Cardiopulmonary failure	0	2 (0.1)	2 (0.1)	2 (0.2)
Febrile neutropenia	0	2 (0.1)	2 (0.1)	0
Gastrointestinal hemorrhage	0	2 (0.1)	2 (0.1)	2 (0.2)
Impaired healing	0	2 (0.1)	2 (0.1)	1 (0.1)
Leukopenia	0	2 (0.1)	2 (0.1)	0
Myocardial infarction	0	2 (0.1)	2 (0.1)	0
Pulmonary embolism	0	2 (0.1)	2 (0.1)	1 (0.1)
Pyrexia	0	2 (0.1)	2 (0.1)	1 (0.1)
Renal failure acute	0	2 (0.1)	2 (0.1)	5 (0.4)

Respiratory failure	0	2 (0.1)	2 (0.1)	0
Sepsis	1 (0.3)	1 (0.0)	2 (0.1)	1 (0.1)
Skin bacterial infection	2 (0.6)	0	2 (0.1)	0
Subcutaneous abscess	0	2 (0.1)	2 (0.1)	0
Toxicity to various agents	1 (0.3)	1 (0.0)	2 (0.1)	0
Source: ADAE data set analysis				

With regards to SAEs that in the opinion of the investigator were treatment related, in trial DUR001-303, patients who received a single dose of dalbavancin (N=349) experienced no treatment related SAEs, whereas, in the two dose group, 2 patients had treatment related SAEs. Treatment related SAEs in DUR001-303 trial are described below in **Table 34**.

In patients who received 2 doses of dalbavancin in pooled phase2/3 trials (N=2124), treatment related SAEs included cellulitis, *Clostridium difficile* colitis, anaphylactoid reaction, and urticaria, 1 patient (<0.1%) each; and 2 cases (<0.1%) of leukopenia. For patients who received a comparator, treatment related SAEs comprised 2 (0.2%) patients with renal failure acute, and 1 (0.1%) patient each with cellulitis, pancytopenia, thrombocytopenia, gastrointestinal disorder, pancreatitis acute, face edema, and nephropathy toxic.

Table 34	**Treatment *Related* Serious Adverse Events : DUR001-303**				
Study/ Patient ID	Preferred Term	start/ stop day	Study Drug Discontinuation	Outcome	Narrative
Dalbavancin 2 doses					
DUR001-303- (b) (6)	*C. difficile* colitis	7/35	No	Recovered	34 year old woman with PMH of obesity, gestational DM, prior MRSA infection, esophageal reflux disease, diverticulosis with intermittent constipation and hepatic steatosis developed diarrhea 4 days after the second dose of dalbavancin and had PCR of stool positive for *C. difficile* and required admission to the hospital. *Medical Reviewer's Comment: The reviewer agrees with the investigator's assessment. C. difficile colitis is known to occur after exposure to antibacterial drugs. This case was possibly related to the study drug.*
DUR001-303- (b) (6)	Urticaria	10/17	No	Recovered	43 year old woman with no significant PMH developed a generalized macular itchy rash on day 9 requiring treatment with IV steroids and intramuscular anti-histamines, resulting in prolongation of hospitalization. Patient was also on concomitant medications (dexketoprofen and nimesulide, both known to cause urticaria) that were given up to 6 days before the event, and sodium thiosulphate, given from day 1-3 for allergic reactions and "intoxication" of uncertain etiology. *Medical Reviewer's Comment: Causality of this case is indeed confounded by concomitant medications and possible underlying disease which is not known. Sodium thiosulphate is usually given for treatment of cisplatin nephrotoxicity or dermatomyositis. It is not known why patient received this drug besides allergic reactions and "intoxication" of unknown etiology. However possibility of study drug as a cause of this SAE cannot be ruled out.*
PMH: Past medical history; DM – diabetes mellitus; C. difficile: *Clostridium difficile; PCR: polymerase chain reaction* Source: Clinical study report, trial DUR001-303					

Medical Reviewer's Comment: After review of the adverse events that were considered related to study drug in trial DUR001-303, this reviewer agrees with the Investigators' determinations of relatedness for events.
Overall based on the available data, it appears that there was no significant difference in terms of SAEs in dalbavancin two-dose arm compared to single dose. Also, when comparing dalbavancin any dose vs the comparator, number of SAEs were almost similar. The median durations of TEAEs related or unrelated, were also similar across treatment groups. Overall, median durations for TEAEs were 3 days in each treatment group.

7.3.3 Dropouts and/or Discontinuations

In trial DUR001-303, the most common reason for study drug discontinuation in both groups were adverse events, and the most common reason for withdrawal from study in both groups was loss to follow-up. Overall, 24 patients (6.9%) in the single-dose group and 21 patients (6.0%) in the two-dose group discontinued study drug, and 26 patients (7.4%) in the single-dose group were withdrawn from the study, versus 27 patients (7.7%) in the two-dose group. (**Table 35**)

Table 35 Dropouts and Discontinuations : Trial DUR001-303 (Safety Population)

	Single Dose (N = 349)	Two-dose (N=346)	Single Dose (N = 349)	Two-dose (N=346)
REASON	**Discontinued Study Drug n=24 (6.9%)**	**Discontinued Study Drug n=21 (6.0%)**	**Withdrawn from study n=26 (7.4%)**	**Withdrawn from study n=27 (7.7%)**
Adverse Event	6 (1.7%)	5 (1.4%)	2 (0.6%)	1 (0.3%)
Death	None	1 (0.3%)	1 (0.3%)	1 (0.3%)
Lack of Efficacy	3 (0.9%)	1 (0.3%)	N/A	N/A
Pregnancy	N/A	N/A	None	1 (0.3%)
Lost to Follow up	5 (1.4%)	5 (1.4%)	14 (4.0%)	14 (4.0%)
Withdrew Consent	2 (0.6%)	2 (0.6%)	5 (1.4%)	3 (0.9%)
Other	8 (2.3%)	7 (2.0%)	4 (1.1%)	6 (1.73%)
Source: ADAE data set				

There were 3 subjects withdrawn from the study due to AEs, 2(0.6%) in the single dose group and 1 (0.3%) in the two dose group. Of 2 subjects in the single dose group who were withdrawn due to adverse events, 1 subject had peripheral ischemia and gangrene, and the other had deep vein thrombosis and phlebitis. The subject from the two dose group was withdrawn from the trial due to an AE of necrotizing fasciitis. All these AEs were severe, and were not related to study drug. Further exploration of reasons in the category "other" is described in the **Table 36** below.

Table 36 Reason for Withdrawal from the Study in Category" OTHER": Trial DUR001-303	
Dalbavancin Two-dose	
SUB-ID	**Reason**
(b) (6)	Progression of Infection/ Sepsis
	Toxicogenic Diphtheria growth
	Lost to Follow up
	Gram negative bacteremia
	Incarceration
	Gram negative bacteremia
Dalbavancin Single Dose	
SUB-ID	**Reason**
(b) (6)	Non-Hodgkin's Lymphoma
	Gram negative bacteremia
	Yeast growth in blood culture
	Lost to Follow up
Source: FDA Medical reviewer's information request from the Applicant	

There were 3 subjects in the single dose group and 1 subject in the two dose group who were discontinued from the study drug due to lack of efficacy. (**Table 37**)

Table 37 Brief narrative of Cases Discontinued from Study Drug due to Lack of efficacy Trial DUR001-303	
Single Dose	
SUBJECT-ID	**Details**
(b) (6)	43 y/o WF, Injection drug user, from US site, had Wound Infection. She also had wound debridement. Culture grew: *Streptococcus intermedius* with MIC 0.02. The patient was started on antibiotics Bactrim and Keflex on study day 4 due to worsening of infection.
	81 y/o WF, with H/O multiple comorbidities, from Rest of the world site, had Major Cutaneous Abscess, also had I&D. Culture grew Gram negative bacteria, *Fusobacterium necrophorum.*
	58 y/o, WM, with H/O HTN, and Psoriasis, from US site had Cellulitis. Culture grew Staphylococcus *aureus* with two different MICs: 0.03, and 0.06. Patient was started on antibiotic Bactrim on study day 4, due to worsening of infection.
Two-dose	
(b) (6)	45 y/o WM, with H/O Chronic Hepatitis C, Injection drug user, from US site with Major Cut Abscess. He had I&D. Culture grew *Staphylococcus aureus with* MIC 0.06. On study day 4, patient was started on Bactrim and Keflex due to worsening of symptoms.
WF –white female; WF – white male. Source: FDA Medical reviewer analysis of ADSL, ADMH, AXPATH and PATHSPAH data set	

The percentages of patients with AEs (deaths included) leading to discontinuation of study drug were low and similar across treatment groups: 6 patients (1.7%) in the single dose group and 5 patients (1.4%) in the two dose group. The AE that led to discontinuation of study drug for >1 patient within a treatment group was generalized rash (2 patients in the two-dose group); hypersensitivity and urticaria occurred in 1 patient in each treatment group (**Table 38**). There were 4 patients for whom the respective AEs that led to

discontinuation of study drug were serious (SAEs). Three patients in the single dose group (1 patient each with hyperglycemia, sepsis, and skin bacterial infection) and 1 patient in the two dose group with necrotizing fasciitis.

Table 38 Adverse Events Leading to Discontinuation of Study Drug		
	Dalbavancin Treatment Group, n (%)	
System Organ Class	**Single-Dose (N=349)**	**Two-Dose (N=346)**
Number of events	7	5
Patients with at least event	***6 (1.4)***	***5 (1.4)***
Immune system disorders	1 (0.3)	1 (0.3)
Hypersensitivity	1 (0.3)	1 (0.3)
Infections and infestations	2(0.6)	1 (0.3)
Necrotizing fasciitis *	0	1 (0.3)
Sepsis *	1 (0.3)	0
Skin bacterial infection *	1 (0.3)	0
Metabolism and nutrition disorders	1 (0.3)	0
Hyperglycemia *	1 (0.3)	0
Respiratory, thoracic, and mediastinal disorders	1 (0.3)	0
Dyspnea	1 (0.3)	0
Skin and subcutaneous tissue disorders	1 (0.3)	3 (0.9)
Generalized rash	0	2 (0.6)
Urticaria	1 (0.3)	1 (0.3)
Vascular disorders	1 (0.3)	0
Flushing	1 (0.3)	0
* *Serious adverse events*		

Narratives for patients in trial DUR001-303 with TEAE who discontinued study drug prematurely due to adverse events is provided in **Table 39** below.

Overall in pooled analysis of phase 2/3 trials, 64 patients (2.6%) who received any dose of dalbavancin [6 patients (1.7%) who received a single dose of dalbavancin, 58 patients (2.7%) who received 2 doses of dalbavancin], and 35 patients (2.9%) who received a control comparator drug, discontinued study medication due to AEs.

Table 39 Patients Who Discontinued Study Drug due to AEs, Trial DUR001-303							
Dalbavancin Two Dose Group (subjects listed received only day 1 dalbavancin dose)							
	SUB-ID	**Age/ Sex/ Race**	**AE/ SAE**	**Duration by Study day**	**Primary Diagnosis**	**Relevant Medical History**	**Brief Narrative Including Event Resolution**
1	(b) (6)	22/F /W	Generalized Rash	1 to 7	Cellulitis	Asthma, seasonal allergies	Generalized rash on day 1, 40 min after a 30 min infusion of dalbavancin 1000 mg. Subject received diphenhydramine, albuterol inhaler, acetaminophen, and oxycodone. Rash resolved on Day 7.
2		71/F /W	Generalized Rash	2 to 14	Cellulitis		Generalized rash on day 2, after receiving infusion of dalbavancin 1000 mg. Subject received chloropyramine and loratadine. Rash resolved on Day 14.
3		81/M /W	Hypersensitivity	1 to 1	Cellulitis		Allergic reaction on day 1, 30 minutes after infusion of dalbavancin 1000 mg. Subject received clemastine, paracetamol, torsemide, and IV saline. Reaction resolved completely in 40 min.
4		31/M /W	Necrotizing Fasciitis	4 to 20	Cellulitis	DM type 1	Subject developed severe anaerobic necrotic fasciitis due to worsening of primary ABSSSI lesion on study day 3 after receiving the 1st dose of dalbavancin 1000 mg. Infection site culture at baseline grew *Streptococcus Agalactiae and b*lood culture grew *micrococcus* and *propionobacterium.* Rescue antibacterial treatment was started. Fasciitis resolved on Day 20.
5		58/ M/ W	Urticaria	1 to 1	Cellulitis	Allergic reaction to strawberries (skin rash and tongue pruritus), Psoriasis.	Urticaria and pruritus of the face, neck, both axilla, and groin on day 1, 15 min. after initiation of dalbavancin 1000 mg infusion. The infusion stopped and clemastine, dexamethasone, and calcium gluconate IV administered. Urticaria and pruritus resolved in 5.5 hours.

6	(b) (6)	71/F/W	Generalized Rash	2 to 14	Cellulitis		Generalized rash on day 2, after receiving dalbavancin 1000 mg. Subject received chloropyramine and loratadine. Rash resolved on Day 14.
Dalbavancin Single Dose							
1	(b) (6)	24/F/W	Flushing	1 to 1	Cellulitis		Heaviness in chest, shortness of breath and flushing of skin on day 1, four minutes after initiation of dalbavancin 1500 mg infusion. The infusion stopped and diphenhydramine, famotidine, methylprednisolone were administered. All symptoms resolved in one hour.
2		53/F/AA	Urticaria	1 to 3	Cellulitis	Multiple drug allergies (PCN, MTZ, codeine, and flu shot), food allergies	Subject developed Urticaria on day 1, after 6 minutes of dalbavancin 1500 mg infusion. The infusion stopped and famotidine, methylprednisolone, and diphenhydramine administered. Urticaria resolved on Day 3.
3		63/M/AA	Sepsis	5 to 8	Major Cutaneous Abscess	Colon cancer	Subject developed hypotension, sepsis, and increased drainage from the abscess on day 4, after receiving the study drug. Symptoms resolved on day 8.
4		38/M/W	Skin bacterial infection	3 to 5	Cellulitis	Prior MRSA infection	Worsening of primary ABSSSI infection on day 3, after receiving dalbavancin 1500 mg. Rescue antibacterial treatment started and the infection improved on day 5.
5		42/F/W	Hyper-sensitivity	1 to 1	Major Abscess	No history of hypersensitivity reactions	Diffuse erythema without hives, SOB, 6 min after initiation of dalbavancin 1500 mg infusion. The infusion stopped. Subject received IV antihistamines. All symptoms resolved in 2-3 minutes.
6		42/F/AA	Hyper-glycaemia leading to hospitalization	4 to 6	Cellulitis	Uncontrolled DM type 2	The patient was hyperglycemic since day 1. Hyperglycemia worsened on day 4, after receiving dalbavancin 1500 mg leading to hospitalization. Hyperglycemia resolved on day 6.

HTN: Hypertension, DM: Diabetes Mellitus; H/O : History of; y/o : Year Old; M – male; F – female; AA – African American; W – white; SOB – shortness of breath; PCN: Penicillin; MTZ: Metronidazole

Source: Review of CRFs by FDA Medical reviewer

Medical Reviewer's Comment: Proportion of patients who discontinued study drug due to AEs in trial DUR001-303 was similar between the single and two-dose groups. Majority of patients had cellulitis as a baseline infection type. The reasons for patients to be withdrawn from the study were also similar proportionately in two treatment groups.

7.3.4 Significant Adverse Events

The AEs leading to emergent therapy are described in sections 7.3.2.The TEAE leading to treatment discontinuation are described in section 7.3.3 of the review.
Additional safety analysis related to hepatic function abnormalities, hypersensitivity reactions, infusion site reactions, hemorrhages, *Clostridium difficile* associated diarrhea, and ototoxicity were conducted.

7.3.4.1 Hepatic Abnormalities

The predetermined criteria for potentially clinically significant values of liver tests chosen by the Applicant in the study protocol were total bilirubin: >1.5 times the upper limit of the reference range (ULN), AST: >3 times ULN, ALT: >3 times ULN, GGT: >3 times ULN, and Alkaline phosphatase: >3 times ULN.
Changes in liver tests were analyzed for DUR001-303 trial and for all Phase2/3 trials.

In prior Phase 2 and 3 clinical trials, more dalbavancin- than comparator-treated subjects with normal baseline transaminase levels had post-baseline alanine aminotransferase (ALT) elevation greater than 3 times the upper limit of normal (ULN) which is reflected as a Warning in the dalbavancin package insert. In these trials 12 subjects with normal baseline ALT had ALT elevation > 3 x ULN (7 subjects with > 3 x ULN, 3 patients with ALT between 5 and 10 × ULN, 1 subject with ALT > 10 x ULN and 1 subject with ALT > 20 x ULN).

Thus, ALT elevations were specifically analyzed in details for trial DUR001-303. In this trial, among subjects with normal baseline ALT, post baseline ALT elevations were observed in 32 (11.8%) subjects in the single dose group and in 33 (11.9%) subjects in the two dose group. ALT transition profiles for patients with post-baseline ALT shift in Trial DUR001-303 are shown below in **Error! Reference source not found.**.

Table 40 Shift in ALT post Baseline: DUR001-303					
Dalbavancin Single Dose					
	Baseline ALT				
Post Baseline ALT Shift	Normal n=302	> ULN <=2xULN n=39	> 2xULN <=3xULN n =4	>3xULN <=5xULN n=0	>5xULN <=10xULN n=0
Normal or <= ULN	262	5	0	0	0
ALT > ULN <=3xULN	37	30	3	0	0
ALT > 3xULN <=5xULN	0	4	1	0	0
ALT > 5xULN <=10xULN	1	0	0	0	0
ALT >10xULN <=20xULN	1	0	0	0	0
ALT >20xULN	1	0	0	0	0
Dalbavancin Two Dose					
	Baseline ALT				

Post Baseline ALT Shift	Normal n=291	> ULN <=2xULN n=39	> 2xULN <=3xULN n =6	>3xULN <=5xULN n=5	>5xULN <=10xULN n=1
Normal or <= ULN	252	7	0	0	0
ALT > ULN <=3xULN	37	31	5	3	0
ALT > 3xULN <=5xULN	1	0	1	2	1
ALT > 5xULN <=10xULN	1	1	0	0	0
ALT >10xULN <=20xULN	0	0	0	0	0
ALT >20xULN	0	0	0	0	0
Source: FDA Medical Reviewer's ADLB data analysis					

Post baseline ALT elevations of > 3 x ULN occurred in 5 subjects with normal baseline ALT levels. Of those, 2 subjects in the two-dose arm (1 subject with ALT >3 x ULN, and another with ALT >5 x ULN), and 3 subjects in the single dose arm (1 with ALT >5 x ULN, 1 with ALT >10 x ULN and 1 with ALT >20 x ULN) had ALT elevations >3 x ULN (**Figure 14**).

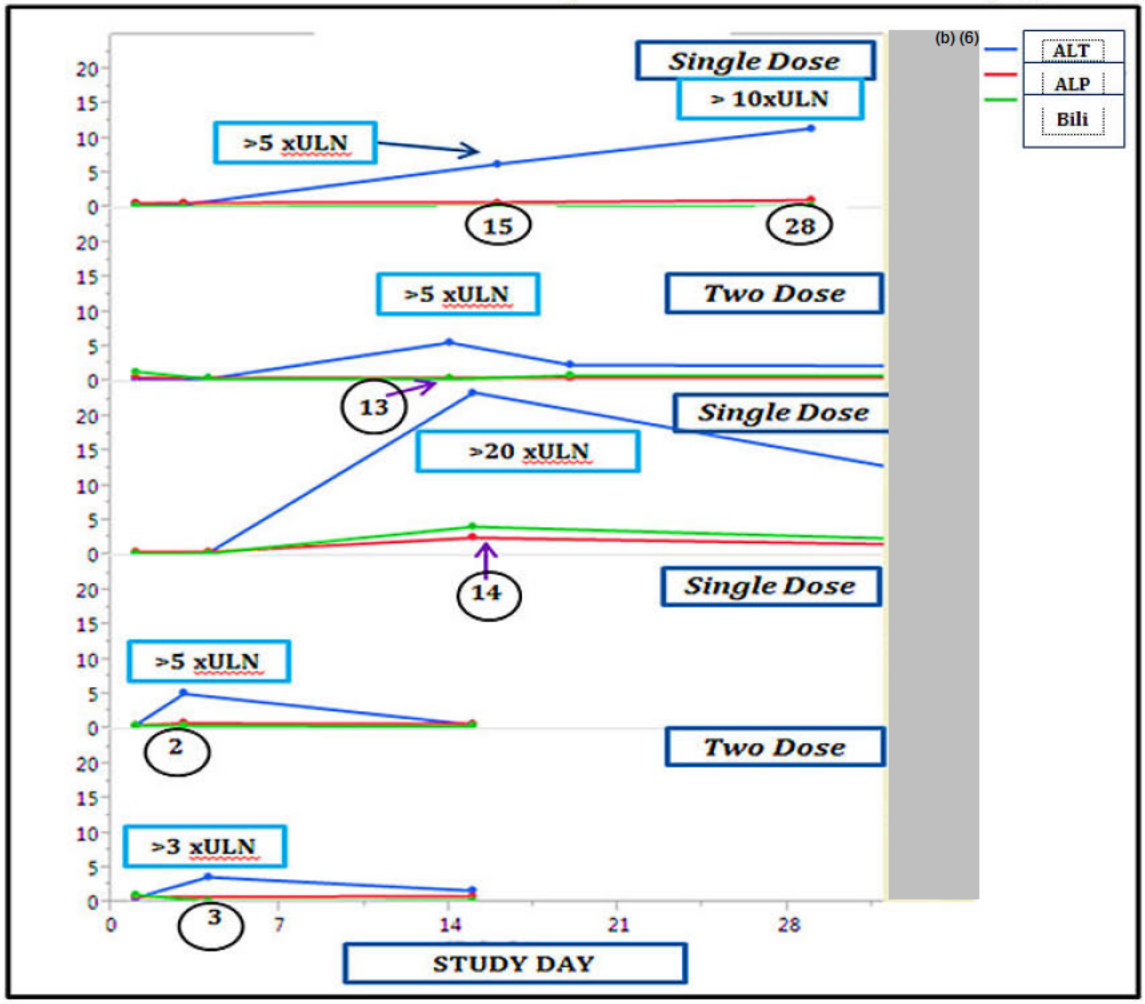

Figure 14 LFTs elevations by study day in subjects with Normal baseline ALT: Trial DUR001-303
(Source: FDA Medical Reviewer's ADLB data analysis)

No patient fulfilled the criteria for Hy's law in dalbavancin trials. However, there was a patient in DUR001-303 trial who, while not formally meeting Hy's law criteria due to a history of liver disease, developed significant concomitant ALT and total bilirubin elevations. This was a 57-year-old white male with a history of ongoing IV drug abuse, smoking of methamphetamine, hepatitis C, alcohol abuse, prior splenectomy and a BMI of 27.2, who was enrolled with right lower leg cellulitis . Concomitant medications included methadone. His liver tests were normal at baseline and at day 4. However, at Day 15, his ALT was found to be >20 x ULN. ALT elevation was associated with an increase in serum total bilirubin to >4 x ULN and elevations in AST and alkaline phosphatase. Liver tests abnormalities were found to be resolved on day 52. Shifts in liver function tests for this subject are presented in **Figure 15** below.

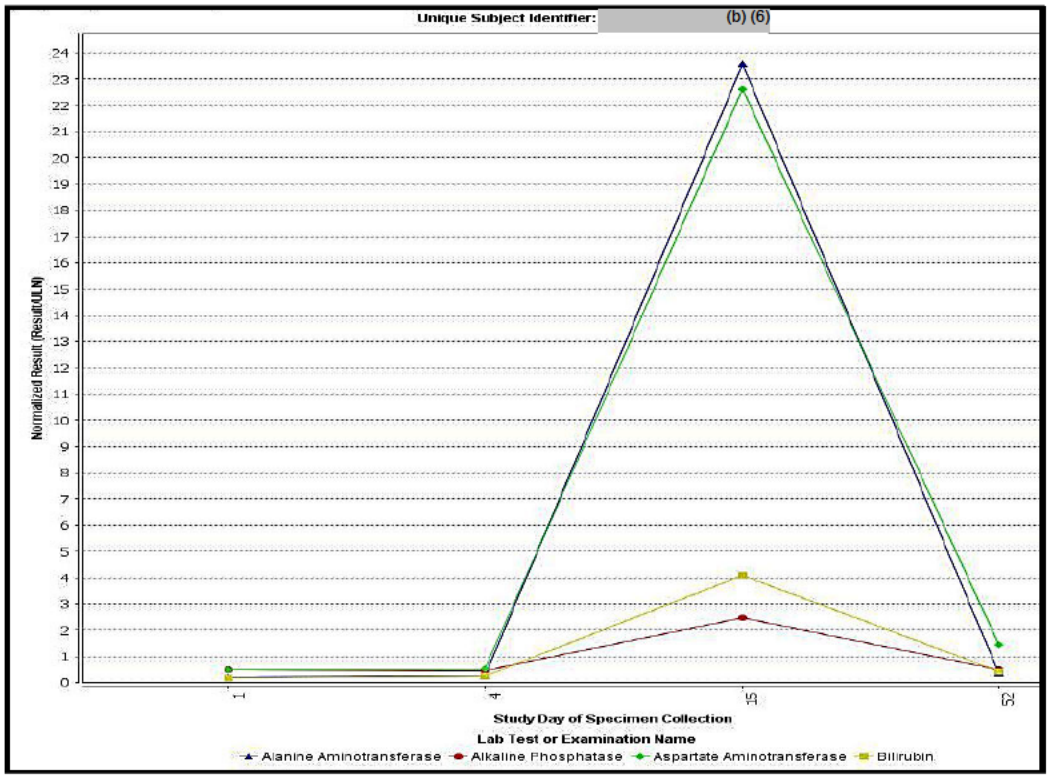

Figure 15 Shift in ALT from normal baseline to >20 x ULN: DUR001-303Trial
Source: FDA Medical reviewer

Medical Reviewer's Comment: Although this subject had concomitant elevations in ALT and serum bilirubin, his underlying medical history is confounded by chronic Hepatitis C, IV Drug abuse, heroin/methamphetamines in toxicology screen, and alcohol abuse. Thus the patient does not fulfil Hy's law criteria.
Hy's Law describes severe liver injury defined as instances of transaminase elevation accompanied by elevated bilirubin (even if obvious jaundice was not present). These cases have been associated with, and have often predicted, post-marketing serious liver injuries

(fatal or requiring transplant). The estimated mortality of such cases is 10%. The rationale here is that hepatocellular injury great enough to interfere with bilirubin excretion) involves a large fraction of the liver cell mass. Per the Guidance for Industry: Drug Induced Liver Injury: Premarketing Clinical Evaluation, July 2009, the criteria for Hy's Law are: 1) ALT or AST >3 x ULN in concert with a serum bilirubin >2 x ULN, without initial findings of cholestasis (i.e. elevated alkaline phosphatase) and, 2) no other reason for these elevations, such as viral hepatitis, pre-existing or acute liver disease, or another drug.

Another subject in previous trial, DUR001-302, subject (b) (6) had concomitant total bilirubin and ALT elevation. The patient was a 47-year-old female with a history of hepatitis C who received 1000 mg and 500 mg of dalbavancin on day 1 and day 8, respectively, for cellulitis. She also received ketorolac on study day 1 and 2 and metamizole on study day 1, both drugs are non-steroidal anti-inflammatory drugs. Her baseline ALT, AST, and total bilirubin levels were normal but ALP level was slightly elevated to 121 (normal range: 35 – 104 U/L). At EOT (day 14) her ALT was found to be > 10x ULN and total bilirubin elevation of > 4x ULN. ALP also increased to >2xULN. ALT elevation subsequently resolved and bilirubin and ALP levels improved by day 27 (For more details, please refer to the NDA 21883 clinical review).

Medical Reviewer's Comment: This subject also had a noticeable concomitant elevation in ALT and total bilirubin. This case also did not meet Hy's Law criteria because of a history of hepatitis C and baseline elevation of alkaline phosphatase. In addition, the subject received ketorolac which could have also caused ALT elevation. Ketorolac is a drug with precautionary warning in patients with impaired hepatic function or a history of liver disease because treatment with ketorolac may cause elevations of liver enzymes and in patients with pre-existing liver dysfunction it may lead to the development of a more severe hepatic reaction.

Additional information on subjects who had normal baseline ALT and had post baseline elevations >3 x ULN in trial DUR001-303 is described in **Table 41**. Of 5 subjects with post baseline ALT >3 x ULN, almost all elevation occurred between study day 3-15 in both single dose and two dose groups.

Similar trend was found in prior phase 2/3 trials, where dalbavancin was used as two dose regimen. Of 12 subjects with normal baseline ALT who had post baseline elevation of > 3 x ULN, most elevations occurred between day 3 -15, except 3 subjects (1 subject had elevation of 7x ULN at day 18, 1 subject had >20 x ULN on day 27, and 1 subject had elevation of 3.4 x ULN on day 29). (**Table 42**)

Table 41 Characteristics of Subjects with Post-baseline ALT Elevations and Normal Baseline ALT, Trial: DUR001-303

	SUBJECT-ID (Diagnosis)	BL-ALT	On Tx-ALT	EOT-ALT	TOC-ALT	Last Value-if any	If other Liver Tests elevated	Medical History
Dalbavancin Single Dose								
1	(b) (6) (LLE WOUND INFECTION)	24	19	**284 [>5 x]**	**516 [11.4 x]**	---		Chronic HCV, IDU, Heroin, methamphetamines, ETOH, and barbiturates in toxicology screen, Acetaminophen, BMI of 28
		Day 0	*Day 2*	***Day 15***	***Day 28***			
2	(b) (6) (RLE CELLULITIS)	10	12	**1061 [23.5 x]**	---	20	-Total Bili: 5 on D-14 [BL: 0.2]; ALP: 320 on D-14 [BL:63]	Chronic HCV, IDU, ETOH abuse, Heroin, methamphetamines in toxicology screen, H/O splenectomy in past.
		Day 0	*Day 3*	***Day 14***		*Day 51*		
3	(b) (6) (RLE CELLULITIS)	24	**228 [5x]**	25	---	-----		Obese, DM type 2, CAD, HTN, muscle necrosis / warfarin, metformin, telmisartan, amlodipine ,Paracetamol (Day 2), zopiclone (Day 2-7), and ketoprofen (Day 2-4). Ketoprofen, Acetaminophen
		Day 0	***Day 2***	*Day 14*				
Dalbavancin Two-Dose								
4	(b) (6) (Right Lower Buttock CELLULITIS)	11	16	**252 [5.6 x]**	116	21		Heavy ETOH intake prior to EOT visit /Opiates, Acetaminophen; aztreonam (D 1-13), metronidazole (D 1-14), amoxicillin (D 1), acetaminophen with hydrocodone (D 1), and acetaminophen (D 2).
		Day 0	*Day 3*	***Day 13***	*Day 18*	*Day 223*		
5	(b) (6)	30	**165 [3.6x]**	76	-----	-----		/Nimesulide, Ketoprofen
		Day 0	***Day 3***	*Day14*				

** Study Day- Day from start of Tx; ALP- Alkaline phosphatase; BL- Baseline; HCV- Hepatitis C; IDU- IV drug abuser; ETOH- Alcohol abuse; NASH- Nonalcoholic staetohepatitis.; H/O- History of; DM- Diabetes mellitus; HTN- hypertension; Normal ALT range: 0 - 45 ; LLE-Left lower extremity; RLE- Right lower extremity;
Source: FDA Medical Reviewer generated table from ADLB data set

Table 42 Characteristics of Subjects with Post-Baseline ALT Elevations and Normal Baseline ALT, Integrated Phase2/3 Trials (Excluding Trial DUR001-303)

	SUBJECT-ID	BL-ALT	On Tx-ALT	EOT-ALT	TOC-ALT	Last Value-if any		If other Liver Tests elevated	Medical History
Trial DUR001-302 : Dalbavancin Two-dose									
1	(b) (6)	29	28	**589 [13 x]**	N/A	*127*	43		Chronic HCV, IDU, Morphine/Methadone in toxicology screen, ETOH abuse
		Day 0	*Day 3*	***Day 14***		*Day 20*	*Day 70*		
2		28	31	**177 [3.9x]**	N/A	N/A			Chronic HCV, IDU
		Day 0	*Day 3*	***Day 14***					
3		34	26	**175 [3.8 x]**	13	N/A			Heavy ETOH use with elevated CDT at BL; BMI : 26.7
		Day 0	*Day 3*	***Day 15***	*Day 32*				
4		19	22	**622 [4.8x]**	41	N/A			Chronic HCV, Cholecystitis, choledocholithiasis/ Metamizole, Ketorolac
		Day 0	*Day 3*	***Day 14***	*Day 27*				
5		11	**148 [3.3x]**	19	N/A	N/A			Chronic Hepatitis B
		Day 0	***Day 3***	*Day 16*					
6		33	**274 [6x]**	17	N/A	45			Heavy ETOH use with elevated CDT at BL.
		Day 0	***Day 3***	*Day 14*		*Day 97*			
Legacy Trials : Dalbavancin Two-dose									
7	(b) (6)	14	**148 [3.7x]**	51	31	N/A			Acetaminophen; Rofecoxib

	(b) (6)	Day 0	**Day 8**	Day 15	Day 27			
8		14 Day 0	N/A	16 Day 8	**953 [20x]** **Day 27**	***317 [7x]*** ***Day 35***		Alcoholic hepatitis
9		57 Day 0	**273 [4.2x]** **Day 8**	144 [2.2x] Day 16	66 Day 29	N/A		NASH [BMI = 26.9; HTN, hyperglycemia], /Aztreonam; Metronidazole; Acetaminophen
10		63 Day 0	N/A	129 [2x] Day 6	**481 [7.4x]** **Day 18**	N/A		NASH [Morbid obesity (BMI = 44.6), HTN, hyperglycemia]/ Acetaminophen; Imipenem.
11		25 Day 0	24 Day 7	102 Day 20	**153 [3.4x]** **Day 29**	N/A		ETOH abuse; / Acetaminophen
12		21 Day 0	**184 [3.6x]** **Day 9**	90 [1.7x] Day 14	N/A	N/A		NASH [BMI=30.2; HTN; hyperglycemia]/ Acetaminophen

** Study Day: Day from start of Tx; ALP: Alkaline phosphatase; BL: Baseline; N/A: Not Available; HCV: Hepatitis C; IDU: IV drug abuser; ETOH: Alcohol abuse; NASH: Nonalcoholic staetohepatitis; Normal ALT range: Varied from 31- 61 in these studies based on Laboratory. Value x ULN is denoted in parentheses[ ] ;
Source: FDA Medical reviewer generated table from ADLB , ADMH data set

Post baseline ALT elevations of > 3 x ULN, irrespective of baseline values occurred in total of 15 subjects in DUR001-303 trial. Of those, 8 subjects in single dose group (5 patient with ALT >3 × ULN, 1 patient with ALT between 5 -10 × ULN, 1 patient with ALT between 10-20 × ULN, 1 patient with ALT >20 × ULN), and 7 patients in two dose group (5 patients with ALT >3 × ULN, and 2 patients with ALT between 5 -10 × ULN) had post baseline ALT elevations of > 3 x ULN. ALT transition profiles for patients who had post-baseline ALT shift in Trial DUR001-303 are shown below. (**Table 43**)

Table 43 Shift in ALT post Baseline: DUR001-303					
Dalbavancin Single Dose					
	Baseline ALT				
Post Baseline ALT Shift	Normal n=302	> ULN <=2xULN n=39	> 2xULN <=3xULN n =4	>3xULN <=5xULN n=0	>5xULN <=10xULN n=0
Normal or <= ULN	262	5	0	0	0
ALT > ULN <=3xULN	37	30	3	0	0
ALT > 3xULN <=5xULN	0	4	1	0	0
ALT > 5xULN <=10xULN	1	0	0	0	0
ALT >10xULN <=20xULN	1	0	0	0	0
ALT >20xULN	1	0	0	0	0
Dalbavancin Two Dose					
	Baseline ALT				
Post Baseline ALT Shift	Normal n=291	> ULN <=2xULN n=39	> 2xULN <=3xULN n =6	>3xULN <=5xULN n=5	>5xULN <=10xULN n=1
Normal or <= ULN	252	7	0	0	0
ALT > ULN <=3xULN	37	31	5	3	0
ALT > 3xULN <=5xULN	1	0	1	2	1
ALT > 5xULN <=10xULN	1	1	0	0	0
ALT >10xULN <=20xULN	0	0	0	0	0
ALT >20xULN	0	0	0	0	0
Source: FDA Medical Reviewer's ADLB data analysis					

The Applicant performed an analysis of ALT elevations on day 3 for patients in the two treatment groups from trial DUR001-303, to understand whether an increased exposure to dalbavancin concentrations (both AUC and Cmax) in the single-dose versus the two-dose treatment groups had an effect on ALT elevations post-baseline. The frequency of post-baseline ALT elevations on day 3 in the single-dose group was marginally lower than that observed in the two-dose group, although patients in the single-dose group received 50% more dalbavancin than those in the two-dose arm (**Table 44**).

Table 44 Patients with Elevations in Alanine Transaminase on Day 3		
	Dalbavancin Treatment Group	
ALT Category	**Single-Dose, n/N (%)**	**Two-Dose, n/N (%)**
> ULN	54 /345 (15.65)	58 /342 (16.96)
> ULN up to 3 x ULN	51 /345 (14.78)	54 /342 (15.79)
> 3 x up to 5 x ULN	2 /345 (0.58)	4 /342 (1.17)
> 5 x up to 10 x ULN	1 /345 (0.29)	0

> 10 x up to 20 x ULN	0	0
> 20 x ULN	0	0
Source: Applicant's table : Clinical study report, DUR001-303		

Medical Reviewer's Comment: It should be noted that ALT elevations were frequently observed from study day 3-15 so the sensitivity of this analysis at day 3 in terms of correlation of dalbavancin exposure and ALT elevations may be limited.

Applicant also presented a correlation between BMI and ALT elevation at baseline in dalbavancin trials. The hypothesis was that obesity, defined as BMI > 25 kg/m^2, would be associated with elevations in ALT values. Below is the Applicants graph (**Figure 16**) showing correlation between BMI >25 kg/m^2 and increases in ALT values > 3x ULN. Applicant provides the justification that patients with elevated BMI are predisposed to NASH and that enrollment of a significant number of patients with obesity in dalbavancin program (Dalbavancin: 1732/2473 [70.0%]; Comparator: 841/1224 [68.7%]), could have contributed to ALT elevations.

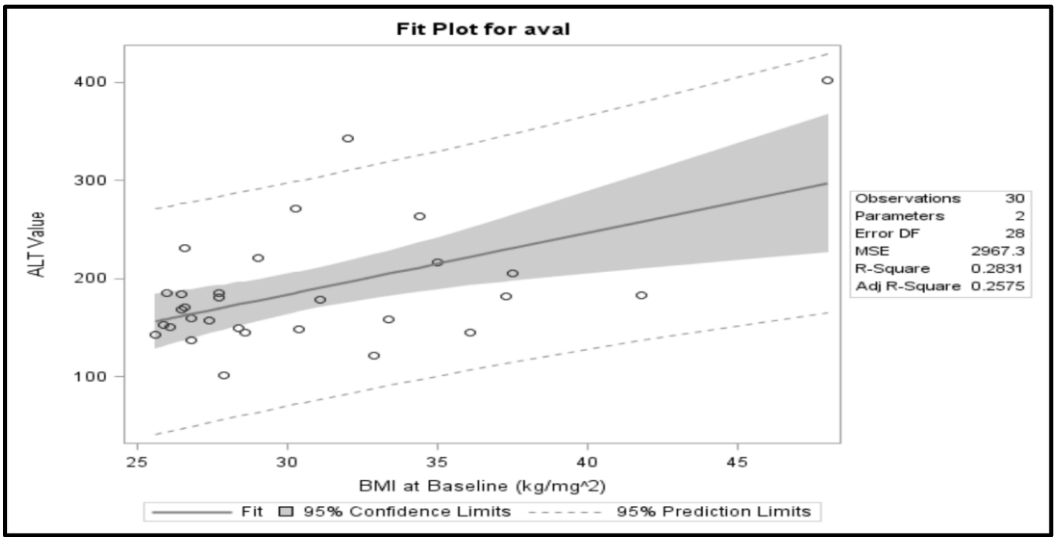

Figure 16 Applicant's Analysis of Correlation of BMI with elevated ALT values
Source: ISS, Figure 7

Medical Reviewer's Comment: Overall, proportion of subjects with normal baseline ALT who had post baseline elevation was similar between two groups (13.2% vs 13.4% in single and two dose group respectively). Likewise, proportion of subjects with abnormal baseline ALT had similar proportion of subjects with post baseline abnormality (88.4% vs 86.3% in single and two dose groups respectively). Notably, in both arms, higher proportions of patients with normal baseline ALT had elevated post baseline values compared to patients with abnormal values at baseline.

It should be noted that most patients who had ALT elevations post dalbavancin exposure had normal ALT at baseline. The risk of developing hepatotoxicity involves a complex interplay

between the chemical properties of a drug, environmental factors (e.g., the use of concomitant drugs or alcohol), age, sex, underlying diseases (e.g., HIV, HCV, HBV, diabetes mellitus), and genetic factors, all of which could lead to hepatotoxicity in a susceptible patient.

Proportions of patients with obesity were similarly distributed between dalbavancin and comparator arm in prior trials. Additional searches of the Medical History (ADMH) datasets for DUR001-303 trial and Phase 2/3 integrated data set was conducted by this reviewer for patients who had elevated post baseline ALTs to explore further. Overall, there was no imbalance in baseline conditions potentially associated with liver disease between dalbavancin single dose and two-dose arm, as well as the comparator.

Overall, based upon the review of ALT elevations in dalbavancin trials, hepatocellular injury associated with dalbavancin use cannot be ruled out. Of note, there were no liver-related deaths reported in any treatment group in dalbavancin trials. It is also noteworthy that liver findings tended to occur within the study day 3 to 35 days of dalbavancin administration implying their temporal relationship to dalbavancin exposure. All 5 patients who developed ALT>3xULN had elevations within first 15 days of drug exposure. Of 12 patients in the previous trials, who developed ALT levels > 3 times ULN, 9 developed the elevations within the first 15 days of exposure to dalbavancin. Most patients returned to within the normal range without intervention. Since dalbavancin is administered for a relatively short time, a phenomenon of adaptation cannot be evaluated here.

Dalbavancin have been found to cause at least transient elevations of aminotransferases, especially ALT, indicating probable hepatocellular injury, with a few cases showing some functional disturbance as indicated by rising serum bilirubin concentration, but no cases of Hy's law or liver failure have yet been attributed to the drug. It is somewhat reassuring that despite marketing of dalbavancin since its approval in May 2014, neither post marketing reports from the sponsor, nor published cases of liver failure associated with the drug have been reported.

From medical reviewer's perspective, it is plausible that at least mild liver injury may be caused by dalbavancin especially in patients with underlying liver disease, or on drugs with potential to cause liver injury. Therefore, the warning for physicians included in the dalbavancin package insert should not be removed. The warning informs physicians that more DALVANCE- than comparator-treated subjects with normal baseline transaminase levels had post-baseline alanine aminotransferase (ALT) elevation greater than 3 times the upper limit of normal in Phase 2 and 3 clinical trials.

7.3.4.2 Hypersensitivity Reactions

The adverse event datasets for dalbavancin DUR001-303 trial was searched for preferred terms related to hypersensitivity reactions. For this analysis, potential allergic reactions were recorded from the immune system disorder SOC, selected terms from the SOC skin

and subcutaneous tissue disorders, gastrointestinal disorders, vascular disorders, injury/poisoning/ procedural, and nervous system disorders.

The search demonstrated that the proportions of subjects with preferred terms that may indicate allergic reactions was similar in the dalbavancin single dose arm, 16/349 (4.6%) compared to two-dose arm, 13/346 (3.8%), (**Table 45**).

Prior ABSSSI trials (DUR001-301, and -302) reported one case of anaphylaxis and DRESS syndrome each in subjects who received dalbavancin. Interestingly no cases of anaphylactic reaction or DRESS syndrome were found in DUR001-303 trial. Overall in all prior phase2/3 trials, number of subjects with preferred terms that may indicate allergic reactions were slightly higher in the comparator as compared to dalbavancin arm, 140 (7.9%) vs. 115 (9.4%), however, proportionately there was no significant difference.

Table 45 Adverse Events Related to Hypersensitivity Reactions

	DUR001-303 Trial Dalbavancin Groups		All Phase 2 and 3 Trials (excluding DUR001-303)	
	Single dose N=349	Two-dose N=346	Dalbavancin N=1778	Comparator N=1224
Total	**16 (4.6%)**	**13(3.8%)**	**140 (7.9%)**	**115 (9.4%)**
Asthenia	0	1 (0.3%)	0	0
Allergic edema	0	0	1 (<0.1%)	0
Anaphylactoid reaction	0	0	1 (<0.1%)	0
Bronchospasm	0	0	0	1 (<0.1%)
Dermatitis	0	1 (0.3%)	1 (<0.1%)	2 (0.2%)
Dermatitis allergic	0	1 (0.3%)	2 (0.1%)	3 (0.2%)
Drug eruption	0	0	2 (0.1%)	0
Drug hypersensitivity	0	0	0	1 (<0.1%)
DRESS *	0	0	1 (<0.1%)	0
Eosinophil percentage increased	0	0	1 (<0.1%)	0
Eosinophilia	0	0	7 (0.4 %)	5 (0.4%)
Eye irritation	0	0	3 (0.17%)	0
Eye pruritus	0	0	1 (<0.1%)	0
Eye swelling	0	0	2 (0.1%)	0
Face edema	0	0	0	1 (<0.1%)
Flushing	2 (0.6%)	0	4 (0.2%)	8 (0.7%)
Food allergy	0	0	2 (0.1%)	0
Generalized erythema	0	0	0	1 (<0.1%)
Hot flush	0	0	1 (<0.1%)	2 (0.2%)
Hypersensitivity	2 (0.6%)	2 (0.6%)	5 (0.3%)	2 (0.2%)
Idiosyncratic drug reaction	0	0	0	1 (<0.1%)
Infusion related reaction	1 (0.39%)	0		
Infusion site swelling	0	1 (0.3%)		

Infusion site pruritus	0	0	4 (0.2%)	0
Infusion site rash	0	0	1 (<0.1%)	0
Infusion site urticaria	0	0	1 (<0.1%)	0
Injection site pruritus	0	0	2 (0.1%)	0
Pruritus	3 (0.9)	0	32 (1.8%)	35 (2.9%)
Pruritus allergic	0	0	1 (<0.1%)	1 (<0.1%)
Pruritus generalized	3 (0.9)	0	6 (0.3%)	9 (0.7%)
Rash	2 (0.6%)	2 (0.6%)	39 (2.2%)	22 (1.8%)
Rash generalized	0	2 (0.6%)	2 (0.1%)	2 (0.2%)
Rash macular	0	0	2 (0.1%)	2 (0.2%)
Rash maculo-papular	0	0	0	1 (<0.1%)
Rash papular	0	0	1 (<0.1%)	1 (<0.1%)
Rash pruritic	0	0	4 (0.2%)	3 (0.2%)
Red man syndrome	0	0	0	2 (0.2%)
Pruritus tongue	1 (0.3%)	0	0	0
Swelling face	0	0	2 (0.1%)	2 (0.2%)
Swollen tongue	0	0	1 (<0.1%)	0
Urticaria	1 (0.3%)	2 (0.6%)	8 (0.4)	8 (0.7%)
* DRESS - Drug rash with eosinophilia and systemic symptoms Source: ADLB data set analysis by FDA Clinical Reviewer				

Most of the potential allergic reactions were mild to moderate except 2 SAEs in DUR001-303 trial. One case of hypersensitivity in the single dose arm, and 1 case of urticaria in the two-dose arm were considered as SAEs. In both of these cases study drug was discontinued. Study drug was discontinued in 3 (0.86%) cases of potential allergic reaction in single dose arm (one case each of hypersensitivity, flushing and urticaria), and 4 (1.15%) cases in two-dose arm (2 with generalized rash, one case each of hypersensitivity and urticaria). Overall in prior phase2/3 trials, incidences of potential allergic reactions were not significantly different in dalbavancin and comparator arms.

Of note, in a prior dalbavancin trial (DUR001-102, a thorough QT study), one subject who was assigned to receive dalbavancin 1500 mg, had treatment discontinuation due to an AE (Redman syndrome) with onset during study medication administration. This was a 26-year old white female who reported shortness of breath and heaviness in her chest 5 minutes into infusion of dalbavancin when she had received ~350 mg of dalbavancin. Infusion was stopped and resumed in 2 minutes but then stopped again after about 2-minute of infusion. A physical examination disclosed diffuse erythema involving the face, neck, central chest and upper extremities. Urticaria was noted on both upper extremities and neck. There was no facial edema and oral mucosa was normal. No wheezes or rhonchi were appreciated on lung auscultation. The physician determined that the subject had red man syndrome and study drug was discontinued. The subject received 50 mg of diphenhydramine. The event resolved in 45 minutes after appearance of first symptom. No cases of red man syndrome were reported in trial DUR001-303.

Medical Reviewer's Comment: Based on the available safety information, dalbavancin single dose does not appear to increase the risk of hypersensitivity reaction as compared to its two dose regimen.

7.3.4.3 Infusion Site Reactions

Since glycopeptides are known to be associated with infusion site reactions and because of the occurrence of infusion site reactions in prior dalbavancin trials, this category of AEs was reviewed. Another reason for this specific review was pertaining to the dosing regimen of dalbavancin. Since the single dose of 1500 mg was used at once in this trial, an increase in the rate of infusion site reactions was thought to be possible in the single dose group.

For this analysis, potential infusion site reactions were recorded from the SOC category General disorders and administration site reactions, selected terms from the SOC Injury, poisoning and procedural complications.

Interestingly, in DUR001-303 trial, single dose (1500 mg) arm had slightly lower potential infusion site reactions compared to the two-dose (4 events in 3 subjects [0.86%] vs 13 events in 7 subjects [2.02%], in single and two-dose arms respectively). In all other phase 2 and 3 trials combined, there were somewhat proportionately fewer infusion site reactions in dalbavancin arm relative to the comparator arm (51 [2.9%] and 53 [4.3%] in dalbavancin and comparator arm respectively). **Table 46** shows the incidences of potential infusion site reactions in trial DUR001-303 and previous phase2/3 trials.

Table 46 Infusion site reactions in DUR-001-303 and other Phase 2 and 3 Dalbavancin Trials												
	DUR001-303						All Phase2/3 trials (Excluding DUR001-303)					
	Dalbavancin Treatment Groups						Treatment Groups					
	Single Dose (N=349)			Two-Dose (N=346)			Dalbavancin (N=1778)			Comparator (N=1224)		
	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%
Total (preferred terms)	**4**	**3**	**0.9**	**13**	**7**	**2.0**	**51**	**51**	**2.9**	**61**	**53**	**4.3**
Asthenia	0	0	0	1	1	0.3	0	0	0	0	0	0
Chills	0	0	0	5	4	0.2						
Infusion related reaction	1	1	0.3	0	0	0	1	1	0.1	1	1	0.1
Infusion site coldness	0	0	0	0	0	0	2	2	0.1	0	0	0
Infusion site discomfort	0	0	0	0	0	0	1	1	0.1	0	0	0
Infusion site erythema	0	0	0	0	0	0	3	3	0.2	8	8	0.7
Infusion site extravasation	3	2	0.6	5	1	0.3	11	11	0.6	12	11	0.9
Infusion site hematoma	0	0	0	0	0	0	0	0	0	2	2	0.2
Infusion site inflammation	0	0	0	0	0	0	1	1	0.1	1	1	0.1
Infusion site irritation	0	0	0	0	0	0	1	1	0.1	4	2	0.2
Infusion site edema	0	0	0	0	0	0	2	2	0.1	2	2	0.2
Infusion site pain	0	0	0	0	0	0	10	10	0.6	21	16	1.3
Infusion site phlebitis	0	0	0	0	0	0	1	1	0.1	1	1	0.1
Infusion site pruritus	0	0	0	0	0	0	4	4	0.2	0	0	0
Infusion site rash	0	0	0	0	0	0	1	1	0.1	0	0	0
Infusion site reaction	0	0	0	0	0	0	2	2	0.1	3	3	0.2
Infusion site swelling	0	0	0	2	1	0.29	3	3	0.2	4	4	0.3
Infusion site Urticaria	0	0	0	0	0	0	1	1	0.1	0	0	0
Injection site cellulitis	0	0	0	0	0	0	0	0	0	1	1	0.1
Injection site discomfort	0	0	0	0	0	0	1	1	0.1	0	0	0
Injection site hematoma	0	0	0	0	0	0	1	1	0.1	0	0	0

Injection site irritation	0	0	0	0	0	0	1	1	0.1	0	0	0
Injection site pain	0	0	0	0	0	0	1	1	0.1	1	1	0.1
Injection site phlebitis	0	0	0	0	0	0	1	1	0.1	0	0	0
Injection site pruritus	0	0	0	0	0	0	2	2	0.1	0	0	0
Source: FDA Medical Reviewer's ADAE data analysis												

Medical Reviewer's Comment: Dalbavancin single dose does not appear to increase the risk of infusion site reactions compared to dalbavancin two-dose. Moreover, the incidence of infusion site reaction was slightly lower in the single dose group.

7.3.4.4 Hemorrhages

Another safety finding in previous dalbavancin trials was higher incidences of adverse events related to hemorrhages including gastrointestinal and soft-tissue hemorrhages in dalbavancin-treated subjects compared to the comparator, although no on-treatment decrease in platelet count was observed. All the events of hemorrhages were non-fatal.
The safety databases for trial DUR001-303 was searched for possible cases related to hemorrhages by conducting standardized MedDRA queries (SMQ). This SMQ included the preferred terms hemorrhage, hemorrhagic anemia, hematuria, gastrointestinal hemorrhage, melena, hematochezia, upper gastrointestinal hemorrhage, petechiae, vessel puncture site hematoma, epistaxis, and spontaneous hematoma. Only two cases of hemorrhages were found in the SMQ search, 1 in each arm (Vitreous hemorrhage in single dose arm and epistaxis in two-dose arm). Both cases were mild, subjects were on anticoagulants and were assessed by investigators as unrelated to study drug. (**Table 47**)

Table 47	**Adverse Events identified by a narrow MedDRA SMQ as Hemorrhages**		
DUR001-303		***All Phase 2 and 3 Trials (excluding** DUR001-303)*	
Dalbavancin Single dose N=349	Dalbavancin Two- dose N=346	Dalbavancin N=1778	Comparator N=1224
1 (0.3%)	1 (0.3%)	36 (2.6%)	19 (1.6%)
Subjects counted once regardless of the number of events			

Medical Reviewer's Comment: Additional details pertaining to the 2 cases of hemorrhages identified in trial DUR001-303 were further explored. Patient with epistaxis in two-dose arm had underlying polymyalgia rheumatica, diabetes mellitus, chronic renal failure and chronic iron deficiency anemia and was receiving enoxaparin. Patient with vitreous hemorrhage in single dose arm had current medical history of injection heroine abuse, and was on heparin and Coumadin.

In conclusion, medical reviewer agrees with the investigator's assessment that both these cases were unrelated to study drug. Dalbavancin single dose does not appear to increase the risk of hemorrhage compared to dalbavancin two-dose or comparator.

7.3.4.5 *Clostridium difficile*-associated diarrhea (CDAD)

Clostridium difficile is a major causative agent of colitis and diarrhea following antibiotic usage. DUR001-303 trial data were searched for AEs potentially consistent with *C. difficile*-associated diarrhea, standardized MedDRA queries (SMQ) were performed using the preferred terms *C. difficile* diarrhea, antibiotic-associated colitis, *Clostridium difficile* colitis, clostridium colitis, and colitis pseudomembranous.

One case of C*. difficile*-associated diarrhea (SOC Infections and Infestations category) was reported as SAE with moderate severity in the two dose arm of trial DUR001-303. This was a 34 year old woman with past medical history of obesity, gestational diabetes mellitus, prior MRSA infection, esophageal reflux disease, diverticulosis with intermittent constipation and hepatic steatosis, who developed diarrhea 4 days after the second dose of dalbavancin and had polymerase chain reaction (PCR) of stool positive for *C. difficile* and required admission to the hospital. It was assessed by the investigator as possibly related to study drug. Diarrhea started on study day 16 and resolved on study day 35. No cases of CDAD were reported in the single dose arm.

In all previous phase 2/3 clinical trials, there were 4 (0.2%) subjects in the dalbavancin and 1 (0.1%) subject in the comparator arm that were diagnosed with CDAD.

7.3.4.6 Nervous System Disorders

There were no cases of seizures reported as an AE in any dalbavancin trials. DUR001-303 trial data were searched for AEs potentially related to nervous system by standardized MedDRA queries (SMQ) using the preferred terms. There was no significant difference between two arms (11[3%] subjects in single dose arm and 16 [4.6%] in two-dose arm), (**Table 48**). In prior dalbavancin phase 2/3 trials, meaningful difference between the dalbavancin and comparator arms were found with regard to nervous system associated AEs.

Table 48 Nervous System Disorders : Trial DUR001-303				
	Dalbavancin Treatment Groups			
	Single Dose [N=349]		Two-Dose [N= 346]	
	No.* of Events	No.*of Subject	No.* of Events	No.* of Subject
Total n, %	**18**	***11(3%)***	**22**	***16 (4.6%)***
Dizziness	5	4 (1.15%)	0	0
Headache	11	6 (1.72%)	5	4 (1.16%)
Somnolence	2	1 (0.29%)	0	0
Pre syncope	0	0	6	2 (0.58%)
Syncope	0	0	1	1 (0.29%)
Dysgeusia	0	0	1	1 (0.29%)
Anxiety	0	0	2	2 (0.58%)
Tremor	0	0	2	2 (0.58%)
Nightmare	0	0	2	1 (0.29%)
Insomnia	0	0	2	2 (0.58%)
Peripheral Neuropathy	0	0	1	1 (0.29%)
*Number Source: FDA Medical Reviewer's ADAE data analysis				

7.3.4.7 Ototoxicity

Hearing loss, tinnitus, vertigo and dizziness have been associated with glycopeptide antibiotics. In DUR001-303, 4 (1.15%) subjects reported dizziness during the study period in single dose group, whereas none in two-dose group (as mentioned in **Table 48** above, Nervous system disorders).

No audiology studies were conducted in the dalbavancin Phase 3 trials. Applicant has performed audiology studies to evaluate ototoxicity in 6 of the 14 Phase 1 studies (Studies VER001-1, VER001-2, VER001-3, VER001-10, VER001-12, and VER001-13). A total of 105 Phase 1 subjects dosed with dalbavancin have undergone stringent audiologic testing, and the data was submitted with original NDA 21883. The results were not suggestive of any pattern of ototoxic change associated with dalbavancin.

Medical Reviewer's Comment: After the detailed review including medical history, concomitant medications of 4 subjects who reported dizziness in trial DUR001-303, it was found that the patients were on concomitant medications that could result in dizziness. None of these cases appeared to be directly associated with dalbavancin exposure.

7.3.5 Submission Specific Primary Safety Concerns

These are discussed in section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In DUR001-303 trial, incidence of TEAEs was low and similar across two treatment groups. There were total of 115 events in 70 subjects (20%) and 119 events in 69 subjects (19.9%) in the single dose and the two dose group, respectively.

The most common AEs were nausea (3.4% and 2%), followed by vomiting (1.7% vs 1.2%) , headache (1.7% vs 0.9%), diarrhea (1.1% vs 0.6%) and dizziness (1.1% vs 0%) in the single and the two dose group, respectively. **Table 49** below shows TEAEs occurred in ≥1% of subjects in DUR001-303 trial in decreasing frequency by preferred term.

Table 49 Treatment-Emergent Adverse Events observed in ≥1% subjects in decreasing frequency

	Dalbavancin Treatment Groups			
	Single Dose (n=349)		Two-Dose (n=346)	
Number of Events	115		119	
	n	%	n	%
Number of Subjects with at least 1 event	**70**	**20.1%**	**69**	**19.9%**
MedDRA Preferred Term				
Nausea	12	3.4%	7	2.0%
Headache	6	1.7%	4	1.2%
Vomiting	6	1.7%	3	0.9%
Diarrhea	4	1.1%	2	0.6%
Dizziness	4	1.1%	0	0.0%
Cellulitis	1	0.3%	5	1.4%
Chills	0	0.0%	4	1.2%
Localized infection	0	0.0%	5	1.4%
Source: FDA Medical Reviewer's ADLB data set analysis				

In Study DUR001-303, the mean and median durations were similar in the single dose and two-dose dalbavancin treatment groups for both TEAEs and TEAEs related to study drug. In DUR001-303, the median duration of an AE was 3.0 days for both the single and two-dose regimens. The median duration of AEs for patients in any regimen of dalbavancin was 3.0 days relative to 4.0 days for those in the comparator arm.

Medical Reviewer's Comment: Common TEAEs were similar in two-dose and single dose groups except nausea and vomiting, which were observed more frequently in the single dose group as compared to the two-dose group, 3.4% vs. 2%, and 1.7% vs. 0.9%, in single dose and two dose groups respectively.

7.4.2 Laboratory Findings

More dalbavancin- as compared to comparator- treated subjects were found to have significant elevations of liver function tests (>5xULN) in prior trials. Additional search for events related to hepatobiliary disorder was also conducted. No TEAE related to SOC hepatobiliary disorders were reported in DUR001-303. The results of the abnormal liver tests are discussed in section 7.3.4, Significant Adverse Events.

This section summarizes the reported laboratory findings for DUR001-303 trial data and the integrated data from pooled phase 2/3 trials.

7.4.2.1 Hematology Tests Abnormalities

Hematopoietic abnormalities are known to be associated with glycopeptides; therefore, adverse events associated with hematopoietic abnormalities were specifically explored. In DUR001-303, none of the hematopoietic abnormalities were reported as an adverse event, as opposed to previous phase 2/3 trials where cases related to hematologic abnormalities were reported in dalbavancin or comparator arms.
In prior phase 2/3 clinical trials, proportion of leukopenia was similar in dalbavancin and comparator arms (8, 0.4% and 7, 0.6% in dalbavancin and comparator respectively). However, proportion of neutropenia was slightly higher in dalbavanin group (5, 0.3% and 1, <0.1% in dalbavancin and comparator groups respectively).Proportions of thrombocytopenia and pancytopenia was similar in two groups.

In DUR001-303, baseline values for each hematology parameter and the mean change from baseline were similar between two treatment groups. Analysis of hematology laboratory results (including mean hematology values), box plots, scatter plots, and shift tables revealed similar results between treatment groups.
The incidences of Potentially Clinically Significant (PCS) hematology values were low and similar between single dose and two-dose treatment groups. PCS values for selected hematology parameters that were also Potentially Clinically Significant Changes (PCSC) are summarized by visit in **Table 50**.

Leukopenia
Although there were 2 cases (0.1%) of febrile neutropenia compared to 0 cases in comparator and 5 cases of neutropenia (0.3%) compared to 1 case (<0.1%) in comparator group in prior dalbavancin Phase 2/3 trials, no cases of neutropenia or febrile neutropenia were reported in DUR001-303 trial. The mean change from baseline, the percentages of patients with a PCS change in neutrophils or a shift from normal at baseline to low post baseline in neutrophils was similar between the single dose and two-dose groups and was not clinically significant. (**Table 50**)

Thrombocytopenia

In the Previous Phase 2/3 trials, 7 cases (0.4) of thrombocytopenia in the dalbavancin group, including a case of profound thrombocytopenia in a healthy volunteer, and 9 cases (0.7%) of thrombocytopenia in the comparator group were reported. In DUR001-303 trial there were 10 cases (2.8%) of thrombocytopenia in the single dose group and 11 cases (3.2%) in the two dose group. The lowest value of platelet was 100 and 104 in the single dose and the two dose group, respectively. Proportions of patients with PCSC decrease in platelets were low and similar across the treatment groups, as it was in previous dalbavancin trials. (**Table 50**)

Table 50 Potentially Clinically Significant Changes for Selected Hematology Parameters : Phase 2/3 Integrated Databases

Parameter Time point	Dalbavancin Treatment Group			
	Single-Dose n/N (%) *	Two-Dose n/N (%) *	Any-Dose n/N (%) *	Comparator n/N (%) *
Hemoglobin				
Low (≤0.8 × LLN and fold decrease ≥0.25)				
On-Tx	1/319 (0.3)	9/1628(0.6)	10/1947 (0.5)	6/940 (0.6)
EOT	1 /291 (0.3)	7/1805 (0.4)	8/2096 (0.4)	6/1041(0.6)
TOC	0/4	6/924 (0.6)	6/928(0.6)	4/473 (0.8)
WBCs				
Low (≤0.5 × LLN and fold decrease ≥0.75)				
On-Tx	0/300	2/1591 (0.1)	2/1891 (0.1)	2/930 (0.2)
EOT	0/282	1/1789 (0.1)	1/2071 (0.0)	1/1035 (0.1)
TOC	0/3	0/928	0/931	0/473
Neutrophils				
Low (≤0.5 × LLN and fold decrease ≥0.75)				
On-Tx	0/291	1/1459 (0.1)	1/1750 (0.1)	2/844 (0.2)
EOT	1/274 (0.4)	0/1631	1/1905 (0.1)	1/965 (0.1)
TOC	0/3	0/816	0/819	0/415
Platelets				
Low (≤0.6 × LLN and fold decrease ≥0.4)				
On-Tx	2/288 (0.7)	7/1550 (0.5)	9/1838 (0.5)	7/916 (0.8)
EOT	1/278 (0.4)	2/1751 (0.1)	3/2029 (0.1)	4/1018 (0.4)
TOC	0/5	4/912 (0.4)	4/917 (0.4)	1/466 (0.2)

*Number of subjects with both baseline and specified visit evaluation; percentage based on number of subjects with both baseline and visit evaluations; LLN: Lower Limit of Normal;
Source: Adapted from Applicant's Integrated summary of safety, replicated by FDA Medical Reviewer

Overall in all Phase2/3 trials there were no significant difference in the proportion of patients with a shift from normal to either high or low values when comparing dalbavancin and comparator treated patients. The proportion of patients with normal platelet counts that decreased on therapy was similar in DUR001-303 trial, 14/349 (4.0%) in the single dose, and 12/374 (3.2%) in the two-dose group, respectively, and in all phase2/3 trials, 28/1430 (2.0%) and 17/751 (2.3%) in the dalbavancin any dose and comparator group, respectively. The proportion of patients who had normal hemoglobin values at baseline and low values on treatment were also similar for those who received dalbavancin or the comparator, 232/1241 (18.7%) and 128/583 (22.0%), respectively. (**Table 51**)

Table 51 On Treatment Shifts of Hematology Parameters, Pooled Data from 8 Phase 2/3 Trials

		Dalbavancin Any Dose regimen: N=2473				Comparator : N=1224			
			On Treatment Shift						
Baseline		N*	Low n (%)	Normal n (%)	High n (%)	N	Low n (%)	Normal n (%)	High n (%)
Hemoglobin (g/dL)	Low	657	536 (27.9)	121 (6.3)	0	347	305 (32.4)	42 (4.5)	0
	Normal	1241	232 (12.1)	1001 (52.2)	8 (0.4)	583	128 (13.6)	453 (48.2)	2 (0.2)
	High	20	0	11 (0.6)	9 (0.5)	10	0	7 (0.7)	3 (0.3)
Lymphocytes (%)	Low	933	393 (22.8)	529 (30.8)	11 (0.6)	525	241 (27.5)	279 (31.8)	5 (0.6)
	Normal	752	81 (4.7)	645 (37.5)	26 (1.5)	343	35 (4.0)	289 (33.0)	19 (2.2)
	High	35	0	24 (1.4)	11 (0.6)	9	0	7 (0.8)	2 (0.2)
Neutrophils (%)	Low	27	7 (0.4)	19 (1.2)	1 (0.1)	2	0	2 (0.2)	0
	Normal	861	29 (1.8)	753 (45.6)	79 (4.8)	392	10 (1.2)	362 (43.0)	20 (2.4)
	High	763	10 (0.6)	493 (29.9)	260 (15.7)	448	4 (0.5)	277 (32.9)	167 (19.8)
Platelets (103/µL)	Low	184	83 (4.6)	95 (5.3)	6 (0.3)	85	43 (4.7)	40 (4.4)	2 (0.2)
	Normal	1430	28 (1.6)	1216 (67.7)	186 (10.4)	751	17 (1.9)	661 (72.2)	73 (8.0)
	High	182	1 (0.1)	48 (2.7)	133 (7.4)	80	2 (0.2)	22 (2.4)	56 (6.1)
WBC (103/µL)	Low	64	17 (0.9)	43 (2.3)	4 (0.2)	27	9 (1.0)	16 (1.7)	2 (0.2)
	Normal	1045	46 (2.5)	957 (51.7)	42 (2.3)	523	34 (3.7)	464 (49.9)	25 (2.7)
	High	743	5 (0.3)	509 (27.5)	229 (12.4)	379	5 (0.5)	271 (29.2)	103 (11.1)

*N is number of patients with low, normal or high value at baseline, and on treatment; percentage based on number of subjects with both baseline and visit evaluations;
Source: Adapted from Applicant's Integrated summary of safety, replicated by FDA Medical Reviewer

Other AEs potentially associated with bone marrow suppression was selected from ADAE data set by preferred term. Potential AEs were recorded from blood and lymphatic system disorders SOC, and selected terms from the SOC Investigations and Congenital, familial and genetic disorders. In DUR001-303, only 3 AEs were reported which could be potentially related to bone marrow suppression. Anemia was reported in 1 (0.3%) subject in single dose group and 2 (0.6%) subjects in the two dose group. One case of decreased hemoglobin was reported in two dose group. No cases of thrombocytopenia, leukopenia or pancytopenia were reported in this trial.
Overall, in all phase 2/3 trials, AEs which could be potentially associated with the bone marrow suppression was low and similar between dalbavancin and comparator arms. **(Table 52)**

Table 52 Adverse Events Potentially Related to Bone Marrow Suppression: Trial DUR001-303

	DUR001-303		Phase2/3 Integrated data set	
AEs potentially related to BM suppression	**Single-Dose N=349**	**Two-Dose N=346**	**Dalbavancin Any Dose N=2473**	**Comparator N=1224**
Anemia	1 (0.3)	2 (0.6%)	37 (1.5)	20 (1.6)
Leukopenia	0		7 (0.3)	7 (0.6)
Neutropenia	0		5 (0.2)	1 (0.1)
Thrombocytopenia	0		3 (0.1)	8 (0.7)
Pancytopenia	0		1 (0.0)	1 (0.1)
Hemoglobin decreased	0	1 (0.3%)	4 (0.2)	0
Hematocrit decreased	0		2 (0.1)	0
Platelet count decreased	0		2 (0.1)	1 (0.1)
Red blood cell count decreased	0		2 (0.1)	1 (0.1)
Sickle cell anemia with crisis	0		2 (0.1)	0

Medical Reviewer's Comment: In DUR001-303, no cases of thrombocytopenia was reported as AEs. All cases with platelets lower than LLN, were mild in intensity. The lowest platelet count in the study was 104,000 (in two-dose arm) in a patient with chronic hepatitis C, and injection drug use. Based on review of the available data, no safety signals were identified in hematology parameters. It does not appear that there is an association with dalbavancin use (any dose) and thrombocytopenia, neutropenia or pancytopenia.

7.4.2.2 Chemistry Abnormalities

The incidences of subjects with PCS chemistry values, PCSC chemistry values and PCS chemistry values that were also PCSC were low and similar between the treatment groups in DUR001-303 trial.

7.4.2.2.1 Renal Toxicity

Because renal toxicity is known to be associated with glycopeptides and the kidney was a target organ for toxicities in preclinical toxicology studies of dalbavancin, the adverse events related to renal impairment were explored. In prior phase 2/3 dalbavancin trials, 7(0.4%) patients in dalbavancin arm and 12 (1.0%) in comparator arm were reported having adverse events related to SOC category renal disorders.

In DUR-001-303 trial, one AE related to renal failure (acute renal failure) was reported in the two-dose group and none in the single dose group. (Table **53**)

Table 53 Adverse Events Related to Renal Toxicity

	DUR001-303 Dalbavancin Arm		All Phase2/3 Dalbavancin trials [excluding DUR001-303]	
Preferred Term	**Single Dose N=349 n (%)**	**Two-dose N=346 n (%)**	**Dalbavancin N=1778 n (%)**	**Comparator N=1224 n (%)**
Renal failure			5 (0.3)	4 (0.3)
Renal failure acute	0 (0.0)	1 (0.28)	1 (0.1)	6 (0.5)
Renal failure chronic			0 (0.0)	1 (0.1)
Renal function test			1 (0.1)	0 (0.0)
Renal impairment			0 (0.0)	1 (0.1)
Total*	0 (0.0)	1 (0.28)	7 (0.4)	12 (1)

Source: FDA Medical Reviewer's ADLB, ADAE data set analysis

The post baseline changes in Cr from any baseline values in DUR-001-303 were similar in both groups. Similarly, in all phase-2/3 trials there were no significant difference in post baseline Cr value between dalbavancin any dose compared to comparator. (**Table 54**)

Table 54 Post Baseline Changes in Creatinine (with any baseline value)

	DUR001-303		All Phase 2/3 Trials		
	Dalbavancin Regimen		Comparator	Dalbavancin Regimen	
Parameter	**Single Dose**	**Two-Doses**	**Comparator**	**Single Dose**	**Two-Doses**
Post Baseline Cr >ULN					
Creatinine (mg/dL)	60 (17.34%)	57 (16.33%)	174 (14.22%)	15 (4.44%)	161 (11.18%)
Total Subjects	349	346	1224	338	1440
Post Baseline Cr >1.5xULN					
Creatinine (mg/dL)	9 (2.60%)	5 (1.43%)	28 (2.29%)	2 (0.59%)	23 (1.60%)
Total Subjects	349	346	1224	338	1440
Post Baseline Cr >2xULN					
Creatinine (mg/dL)	2 (0.57%)	0 (0.0%)	13 (1.06%)	1 (0.30%)	10 (0.69%)
	349	346	1224	338	1440

Source: FDA Medical Reviewer analysis of ADLB : DUR-001-303 data set and Integrated phase 2/3 data set

In all phase2/3 trials, the proportion of patients with shifts from normal baseline to high Cr values while on treatment were similar between the dalbavancin and comparator groups (54, 2.7% and 31, 3.2% respectively). Similar proportions of patients in the dalbavancin and comparator groups with high serum creatinine values at baseline remained high while on treatment (110/235 [46.8%] and 59/117 [50.4%] respectively). Patients with CrCl at baseline of <30 mL/min or 30 to 59 mL/min showed no increased risk of shifts in creatinine or urea nitrogen levels while on treatment. (**Table 55**)

Table 55 On Treatment Shifts in Renal Function Laboratory Parameters Pooled Data from 8 Phase 2/3 Studies

			Dalbavancin Any Dose, Any Regimen N = 2473			Comparator N = 1224			
			Low	Normal	High		Low	Normal	High
Overall									
		N	n (%)	n (%)	n (%)	N	n (%)	n (%)	n (%)
Creatinine	Low	141	85 (4.2)	55 (2.7)	1 (0.0)	80	45 (4.7)	34 (3.5)	1 (0.1)
mg/dL	Normal	1627	78 (3.9)	1495 (74.6)	54 (2.7)	768	45 (4.7)	692 (71.7)	31 (3.2)
	High	235	1 (0.0)	124 (6.2)	110 (5.5)	117	1 (0.1)	57 (5.9)	59 (6.1)
Baseline CrCl <30 mL/min									
Creatinine	Low	0	0	0	0	0	0	0	0
mg/dL	Normal	8	1 (2.6)	6 (15.8)	1 (2.6)	1	0	1 (6.3)	0
	High	30	1 (2.6)	11 (28.9)	18 (47.4)	15	0	2 (12.5)	13 (81.3)
Baseline CrCl 30-59 mL/min									
Creatinine	Low	2	0	1 (0.3)	1 (0.3)	1	1 (0.6)	0	0
mg/dL	Normal	207	5 (1.4)	182 (52.3)	20 (5.7)	116	4 (2.3)	98 (55.4)	14 (7.9)
	High	139	0	66 (19.0)	73 (21.0)	60	1 (0.6)	29 (16.4)	30 (16.9)

Source: Adapted from ISS Module 5.3.5.3, replicated by FDA Medical Reviewer

In trial DUR001-303 there were very few TEAEs reported in SOC renal disorders. Total of 4 subjects, of which, 1 in the single dose and 3 in the two-dose groups had TEAE associated with renal disorders. One subject in the single dose group had dysuria, whereas in the two dose group, 1 subject had cyst of left kidney, right sided hydronephrosis and urolithiasis, 1 subject had

acute on chronic renal failure, and 1 subject had dysuria and urinary retention. All of these TEAEs were mild to moderate except the case of acute on chronic renal failure. None of these TEAEs led to discontinuation of study drug or were assessed by investigator as treatment related.

Medical Reviewer's Comment: Subject level data on the patient with acute renal failure in the two dose group of DUR-001-303 trial were further explored. This subject had a baseline chronic renal disease with underlying comorbidities of diabetes mellitus, hypertension, and hypercholesterolemia. , She was also on several medications known to worsen chronic renal failure e.g., hydralazine, furosemide, doxazocin, hydrochlorothiazide, and colchicine. It was extremely unlikely that patient's acute renal failure was related to study medication.
In conclusion, based on the available data, dalbavancin single dose does not appear to be associated with nephrotoxicity greater than two-dose regimen. In addition, based upon the review of all phase2/3 trials, dalbavancin at any dose does not appear to be associated with nephrotoxicity greater than the comparator.

7.4.2.2.2 Hyperglycemia and Hypoglycemia

Potentially clinically significant (PCS) hypoglycemia was defined as a glucose level less than 0.6 times the upper limit of normal and folds decrease ≥0.4 at any post-baseline measurement. Hyperglycemia was defined as any elevation in glucose levels and as a glucose level greater than 3 times the upper limit of normal at any post-baseline measurement or elevation in glucose levels > 3 fold from baseline.

The incidence and proportion of subjects with clinically significant hyperglycemia in trial DUR001-303 were very low and comparable between the dalbavancin groups. There were no subjects who met both the criteria for clinically significant hyperglycemia with glucose ≥3 × ULN and fold increase ≥3.0 in either arm. However, there were 6 (1.72%) subjects in the single dose group and 5 (1.44%) in the two dose group who had post baseline glucose increase by ≥3 × ULN. Subjects whose post baseline glucose value increased to > 3 times from baseline value were 2(0.6%) in the single dose group and none in the two dose group (**Table 56**). Similarly in all phase 2/3 trials, there were no significant differences in incidences of hyperglycemia and hypoglycemia between dalbavancin any dose and comparator (**Table 57**).

Table 56	**Potentially Clinically Significant Hyperglycemia and Hypoglycemia Trial DUR001-303 [Safety population]**	
Parameter	**Dalbavancin Single Dose N=349**	**Dalbavancin Two- Dose N=346**
Glucose ≥3 × ULN only		
	6 (1.7%)	**5 (1.4%)**
Glucose value increased to > 3 fold from baseline value		
	1 (0.3%)	**0 (0.0%)**
Glucose Low (≤0.6 × LLN and fold decrease ≥0.4)		

	1 (0.3%)	0 (0.0%)

*Glucose: (mmol/L)
Source: FDA medical reviewer's analysis of ADLB data set DUR-001-303;

Table 57 Potentially Clinically Significant Hyperglycemia and Hypoglycemia: Phase2/3 integrated data set

	Dalbavancin Single-Dose n/N (%)	Dalbavancin Two-Dose n/N (%)	Dalbavancin Any-Dose n/N (%)	Comparator n/N (%)
Glucose High (≥3 × ULN and fold increase ≥3.0)				
On-Treatment	0/329	4/1625 (0.2)	4/1954 (0.2)	1/932 (0.1)
EOT	0/299	3/1825 (0.2)	3/2124 (0.1)	0/1046
TOC	0/6	3/937 (0.3)	3/943 (0.3)	0/468
Glucose Low (≤0.6 × LLN and fold decrease ≥0.4)				
On-Treatment	1/329 (0.3)	1/1625 (0.1)	2/1954 (0.1)	1/932 (0.1)
EOT	0/299	4/1825 (0.2)	4/2124 (0.2)	3/1046 (0.3)
TOC	0/6	0/937	0/943	0/468

Source: ISS Module 5.3.5.6

Other AEs potentially associated with glucose metabolism were selected from ADAE data set by preferred terms. Potential AEs were recorded from metabolism and nutrition disorders SOC, and selected terms from the SOC Investigations. (**Table 58**)

Table 58 Adverse Events Potentially Related to Glucose Metabolism: DUR-001-303 and All Phase2/3 trials

	DUR001-303		All Phase 2/3 studies Integrated	
	Dalbavancin Groups		Study Groups	
	Single Dose (N=349)	Two-dose (N=346)	Dalbavancin Any Dose (N=2124)	Comparator (N=1224)
Hyperglycemia	1 (0.3)	0	25 (1.0)	14 (1.1)
Hypoglycemia	0	0	16 (0.6)	11 (0.9)
Diabetes mellitus	1 (0.3)	0	4 (0.2)	7 (0.6)
Hypoglycemia unawareness	0	0	2 (0.1)	0
Diabetes mellitus inadequate control	0	0	1 (0.0)	0
Glucose tolerance impaired	0	0	1 (0.0)	0
Type 2 diabetes mellitus	0	0	1 (0.0)	0
Blood glucose increased	0	0	10 (0.4)	6 (0.5)
Glucose urine present	0	0	1 (0.0)	1 (0.1)

Source: FDA Medical Reviewer's Analysis, ADLB data set

Potential glucose metabolism associated SAEs in patients who received any dose of dalbavancin comprised of 1 patient (1/2473 = <0.1%) with inadequate control of diabetes mellitus and 1 patient (1/2473 = <0.1%) with hyperglycemia, both of which were not treatment related. Hyperglycemia led to discontinuation of study medication in 1 patient (<0.1%), which was also not treatment related.

Medical Reviewer's Comment: Based on available data, dalbavancin single dose was similar to two-dose in terms of hyper- or hypo- glycaemia incidences. Data from all phase2/3 studies did not show any association of dalbavancin with abnormalities in glucose metabolism.

7.4.2.2.3 Lactate Dehydrogenase

Lactate dehydrogenase (LDH) was measured as a part of laboratory evaluations in dalbavancin clinical trials. The level of LDH ≥ 5 x ULN was pre-specified as a potentially clinically significant.
In DUR001-303, no subject had LDH elevation ≥ 5 x ULN. There was no significant difference in shifts in LDH value post baseline between the single dose and two-dose arms
In the single dose group, 3% of patients had shift from normal baseline value to a high value on day 3, and 2.9% had elevated LDH at the EOT. In the two dose group, 2% of patient had shift from normal baseline value to a high post baseline on day 3, and 3.8% of patients had elevated LDH at EOT. **Table 59** below describes the shifts in LDH. Similarly, in prior phase2/3 trials, there was no significant difference in LDH elevations post baseline between the dalbavancin and comparator arm (14.3% in the dalbavancin group and 11.6% in the comparator group).

Table 59 Shift Table for LDH (Safety Population): DUR001-303

Dalbavancin Single Dose

		On Treatment				EOT				TOC			
	Baseline		**Low**	**Normal**	**High**		**Low**	**Normal**	**High**		**Low**	**Normal**	**High**
Parameter		N *	N (%)	N (%)	N (%)	N(a)	N (%)	N (%)	N (%)	N(a)	N (%)	N (%)	N (%)
LDH (U/L)	**HIGH**	21	0	9 (3.4)	12 (4.5)	18	0	13 (5.4)	5 (2.1)	0	0	0	0
	LOW	5	2 (0.8)	2 (0.8)	1 (0.4)	3	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0	0
	NORMAL	*238*	0	230 (87.1)	8 *(3.0)*	219	1 (0.4)	211 (87.9)	7 *(2.9)*	6	1 (16.7)	5 (83.3)	0

Dalbavancin Two-Dose													
LDH (U/L)	**HIGH**	26	0	12 (4.7)	14 (5.5)	21	0	11 (4.6)	10 (4.2)	1	0	1 (16.7)	0
	LOW	0	0	0	0	0	0	0	0	0	0	0	0
	NORMAL	*228*	0	223 (87.8)	5 *(2.0)*	217	2 (0.8)	206 (86.6)	9 *(3.8)*	5	0	5 (83.3)	0
*Number of subjects with both baseline and specified visit evaluation; percentage based on number of subjects with both baseline and visit evaluations. Low = below lower limit of normal range; Normal = within normal range; High = above upper limit of normal range. On-treatment = Day 3, EOT = End of Treatment. TOC = Test of Cure. Source: Adapted from ISS Module 5.3.5.1, replicated by FDA Medical Reviewer													

Medical Reviewer's Comment: Based on available data, dalbavancin single dose regimen was similar to the two dose regimen in terms of LDH elevations post baseline. None of the subjects had clinically significant elevations in LDH in DUR001-303 trial.

7.4.3 Vital Signs

Vital signs (VS) were performed at baseline, day 1, day 3-4, day 8, day 14-15 and day 28 (+/- 2 days). Measurements of VS included height and weight at baseline visit only and temperature, blood pressure, pulse rate, respiratory rate with all study visits. Change from baseline was calculated for each patient at the specified visit as the value at the specified visit minus the baseline value. VS were also monitored for potentially clinically significant changes (PCSC). The criteria used to identify PCSC in results are presented in **Table 60** below.

Table 60 Criteria for Identifying PCS and PCSC Vital Sign Results					
Parameter (units)	**Normal Range**	**PCS Low Value**	**PCS High Value**	**PCSC Decrease in value**	**PCSC Increase in Value**
Pulse (bpm)	60-100	<50	>120	0.5x	2x
RR (bpm)	---	<8	>32	---	---
SBP(mmHg)	95-145	<85	>200	0.2x	1.6x
DBP(mmHg)	60-95	<50	>120	0.2x	1.2x
Temperature*	---	---	---	2°	2°
*Oral temperature(°Celsius); SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: respiratory rate;					

In trial DUR001-303, there were very few clinically significant shifts in vital signs. Proportionately, there was slightly higher number of patients shifted from normal value to clinically significant diastolic blood pressure in two-dose arm compared to single dose (4 (0.1%) and 11 (1.4%) in the single dose and two dose groups, respectively). Similar proportion of patients shifted to potentially clinically significant values in both arms in terms of systolic blood pressure and pulse rate (**Table 61**, **Table 62**, **Table 63**).

Table 61 Shifts in Diastolic Blood Pressure (DBP): DUR001-303 Trial

	Dalbavancin Single Dose		Dalbavancin Two Dose	
	n	%	n	%
Normal-Normal	321	40.7	318	40.4
Normal-High	4	0.1	11	1.4
Normal-Low	0	0	0	0
Low-Low	0	0	0	0
Low-Normal	21	2.7	15	1.9
Low-High	0	0	0	0
High-Normal	0	0	0	0
High-High	3	0.1	2	0.1
High-Low	0		0	0

Source: FDA Medical Reviewer's analysis of ADVS data set

Table 62 Shifts in Systolic Blood Pressure(SBP): DUR001-303 Trial

	Dalbavancin Two-Dose		Dalbavancin Single dose	
	n	%	n	%
Normal-Normal	250	31.7	264	33.5
Normal-High	56	7.1	48	6.1
Normal-Low	0	0	0	0
Low-Low	0	0	0	0
Low-Normal	7	0.1	5	0.1
Low-High	2	0.1	0	0
High-Normal	0	0	0	0
High-High	31	3.9	32	4.1
High-Low	0	0	0	0

Source: FDA Medical Reviewer's analysis of ADVS data set

Table 63 Shifts in Pulse Rate: DUR001-303 Trial

	Dalbavancin Two-dose		Dalbavancin Single dose	
	n	%	n	%
Normal-Normal	295	37.4	294	37.3
Normal-High	35	4.4	37	4.7
Normal-Low	0	0	0	0
Low-Low	0	0	0	0
Low-Normal	1	0.1	6	0.1
Low-High	1	0.1	0	0
High-Normal	0	0	0	0
High-High	14	1.8	12	1.5

High-Low	0	0	0	0
Source: FDA Medical Reviewer's analysis of ADVS data set				

In all dalbavancin phase 2/3 trials, there were few patients with potentially clinically significant changes in vital sign measurements while on treatment. For patients who received any dose of dalbavancin (n=2473), no patient had a ≥2-fold increase and only 2 patients (0.1%) had a ≥0.5-fold decrease in pulse rate; 1 patient (0.1%) had a ≥1.6-fold increase and 13 patients (0.6%) had a ≥0.2-fold decrease in systolic blood pressure; 28 patients (1.4%) had a ≥1.2-fold increase and 61 patients (3.0%) had a ≥0.2-fold decrease in diastolic blood pressure; and 2 patients (0.1%) had a ≥2° Celsius increase and 350 patients (17.3%) had a ≥2° Celsius decrease in oral temperature. (**Table 64**)

Table 64 Changes from Baseline to On-Treatment for Vital Sign Measurements: All 8 Phase 2/3 Studies

	Dalbavancin Treatment Groups		Treatment Groups	
Event, n/N (%)	**Single-Dose N = 349**	**Two-Dose N = 2124**	**Dalbavancin Any Dose Any Regimen N = 2473**	**Comparator N = 1224**
Pulse (bpm)				
≥2-fold increase	0/340 (0.0)	0/1703 (0.0)	0/2043 (0.0)	0/972 (0.0)
≥0.5-fold decrease	0/340 (0.0)	2/1703 (0.1)	2/2043 (0.1)	1/972 (0.1)
Systolic blood pressure				
≥1.6-fold increase	0/340 (0.0)	0/1703 (0.0)	0/2043 (0.0)	1/972 (0.1)
≥0.2-fold decrease	0/340 (0.0)	13/1703 (0.8)	13/2043 (0.6)	3/972 (0.3)
Diastolic blood pressure				
≥1.2-fold increase	1/340 (0.3)	27/1703 (1.6)	28/2043 (1.4)	14/972 (1.4)
≥0.2-fold decrease	4/340 (1.2)	57/1703 (3.3)	61/2043 (3.0)	33/972 (3.4)
Oral temperature				
≥2° Celsius increase	0/340 (0.0)	2/1683 (0.1)	2/2023 (0.1)	1/957 (0.1)
≥2° Celsius decrease	43/340 (12.6)	307/1683 (18.2)	350/2023 (17.3)	237/957 (24.8)

N = number of patients with data recorded for each event at both baseline and on-treatment
Source: Integrated Summary of Safety (ISS), Table 52;

Medical Reviewer's Comment: No obvious safety signal associated with dalbavancin use and any physical examination findings or vital signs hypertension, hypotension, tachycardia or bradycardia was identified based on available data.

7.4.4 Electrocardiograms (ECGs)

Applicant conducted an expert analysis on reports of ECG results for the Phase 1 and Phase 2/3 integrated analysis sets. No rhythm disturbance, including ventricular arrhythmia, was observed in any of the ECG recordings analyzed.

Of the subjects in the Phase 2/3 integrated analysis set, 354 dalbavancin-treated subjects and 178 comparator-treated subjects had normal T and U waves at Baseline and had a post- Baseline ECG conducted. Of these, 1 (0.3%) dalbavancin-treated subject (Subject (b) (6) had a T-wave abnormality, described as an abnormal T pattern in standard leads, with normal sinus rhythm and a prior myocardial infarction. In comparison, 2 (1.1%) comparator-treated subjects (Subjects (b) (6) had a T-wave abnormality; Subject (b) (6) treated with comparator (vancomycin), had abnormal widespread ST pattern, with normal sinus rhythm; Subject (b) (6) treated with cefazolin, had abnormal widespread T pattern, with normal sinus rhythm. No subject had a U-wave abnormality or both T- and U-wave abnormalities.
An expert report of ECG results for the Phase 2/3 integrated analysis set concluded that no rhythm disturbance, including ventricular arrhythmia, was observed in any of the ECG recordings analyzed. Only slight modification of repolarization, including T-wave morphology, was observed following serial analysis of each subject's ECGs as reported by the Applicant. No change in U-wave amplitude or appearance of new U waves was observed during drug exposure.

In a Thorough QT Trial (TQT), DUR001-102, dalbavancin in IV doses up to 1500 mg did not prolong the QTc interval and had no effect on the heart rate, PR, or QRS interval. These results correspond to a negative TQT study. (Discussed in detail in section 7.4.5, Special Safety Studies/Clinical Trials)

Other Cardiac Disorders

In DUR001-303, a total of 3 subjects were reported to have TEAEs related to cardiac disorders. One in the single dose group (angina pectoris) and 2 in the two dose group (degeneration of aortic valve and stenocardia in 1 subject and arrhythmia in 1 subject). All were mild in intensity and did not lead to study drug discontinuation. Further analysis of the cases concurred with investigator's assessment that TEAES were not related to study drug.

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1 Thorough QT Study (TQT)

The TQT study was reviewed by the interdisciplinary review team (IRT) during NDA21833 review process prior to dalbavancin approval in 2014. A thorough QT study showed that dalbavancin did not prolong the QTc interval.

7.4.5.2 Dalbavancin Coagulation Feasibility Study

Since some glycopeptide antibiotics are known to be associated with artificial prolongation of laboratory coagulation tests including activated partial thromboplastin time, prothrombin time and international normalized ratio (INR), Applicant was suggested by FDA to perform coagulation feasibility study for dalbavancin as a post marketing requirement. Results showed that dalbavancin at therapeutic levels do not artificially prolong prothrombin time (PT) or activated partial thromboplastin time (aPTT). For detailed review of this study, please refer to Clinical Pharmacology Review.

7.4.6 Immunogenicity

Dalbavancin was evaluated for potential immunogenicity in guinea pigs in a standard intradermal sensitization study followed by dermal challenge. No guinea pigs had a positive response to the challenge.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The majority of subjects in phase 2 and 3 trials received a dalbavancin two-dose regimen of 1000 mg on day 1 and 500 mg on day 8 or 1500 mg as a single dose, therefore, explorations for dose dependency for AEs are limited.

Since a significant ALT elevation has been found in dalbavancin trials, the Applicant conducted an analysis of ALT elevations on day 3 in patients in DUR001-303 trial, for the two treatment groups. Overall in dalbavancin trials, dose limiting toxicity or TEAEs has not been reported. One subject in DUR001-302 trial (b) (6) received 3000 mg of dalbavancin but did not experience any TEAEs. In DUR001-104 trial, 6 subjects each received total dalbavancin exposures of 4500 mg (3.0-fold the proposed exposure), 3500 mg (2.3-fold the proposed exposure), and 2500 mg (1.7-fold the proposed exposure) with no TEAEs. Multiple doses of dalbavancin at total exposures of up to 4500 mg administered to healthy subjects in prior studies were well tolerated. (Table 43, Section 7.3.4.1; Hepatic Abnormalities)

7.5.2 Time Dependency for Adverse Events

Dalbavancin is being proposed to be used for an acute infection as a single dose, thus time dependency for AEs is not relevant in this submission.

Overall, in all dalbavancin phase2/3 studies, the mean ± SD time to onset of the first TEAE was 6.2 ± 7.9 days for patients who received any dose of dalbavancin, 4.9 ± 5.7 days for patients who received a single dose of dalbavancin, 6.3 ± 8.1 days for patients who received 2 doses of dalbavancin, and 7.2 ± 9.6 days for comparator.

7.5.3 Drug-Demographic Interactions

7.5.3.1 TEAEs by Age, Gender, Race and Geographic region

Clinical safety results in the subgroups of subjects from trial DUR001-303 were analyzed for drug-demographic interactions by age (< 65 years and ≥ 65 years), gender (male and female), race (White and non-White), and country (United States and Rest of the world sites).

In DUR001-303 trial, there was a slightly higher incidence of TEAEs among patients ≥ 65 years of age in the two dose group (20.4%) than in the single dose group (17.1%). In terms of gender, TEAEs occurred in slightly higher proportions of females in the single dose group (23% vs 19% of females in the single dose and two dose groups respectively), whereas slightly higher proportions of males had TEAEs in the two dose group (18% vs 21% males in single and two dose groups respectively). In terms of race, Black patients had slightly higher percentages of TEAE in the single dose group, 28.6% in the single dose vs 16.1% in the two dose group. Patients from US sites had slightly higher proportion of TEAEs in the single dose compared to the two dose group, 27.8% and 24.5%, respectively. Nevertheless, none of these differences were deemed significant (**Table 65**).

Table 65 Drug-Demographic Interaction Treatment-Emergent Adverse Events in Patient Subgroups (Safety Population)

	Dalbavancin Treatment Groups			
	Single Dose, n (%)		Two-Dose, n (%)	
Age	**<65**	**>65**	**<65**	**>65**
	n = 308	**n = 41**	**n = 297**	**n = 49**
Number of events	103	12	100	19
Number of patients with at least 1 event	63 (20)	7 (17)	59 (20)	10 (20)
Gender	**Female**	**Male**	**Female**	**Male**
	n =145	**n =204**	**n =144**	**n =202**
Number of events	59	56	54	65
Number of patients with at least 1 event	34 (23)	36 (18)	27 (19)	42 (21)
Race	**White**	**Black**	**White**	**Black**

	n =312	n =28	n =309	n =31
Number of events	92	17	104	7
Number of patients with at least 1 event	59 (19)	8 (29)	61 (20)	5 (16)
Geographic Region	**US**	**Non-US**	**US**	**Non-US**
	n =158	**n =191**	**n =159**	**n =187**
Number of events	77	38	64	55
Number of patients with at least 1 event	44 (28)	26 (14)	39 (25)	30 (16)

7.5.4 Drug-Disease Interactions

7.5.4.1 Liver Associated Conditions

Since alanine amino transferase (ALT) elevations were of particular concern in dalbavancin trials, association of ALT elevation with underlying liver diseases and baseline hepatobiliary status was examined in the two arms to evaluate drug disease interaction. Proportions of patients with underlying liver associated conditions were similar between the two arms. (**Table 66**)

Table 66 Liver Associated Conditions by Medical History: DUR001-303

	Dalbavancin Treatment Groups	
	Single Dose n=349, n (%)	**Two-Dose n =346, n (%)**
Drug Abuse*	139 (39.8%)	135 (39.0%)
Alcohol Abuse	3 (0.86%)	3 (0.86%)
Hepatitis C and Chronic Hepatitis C	48 (13.75%)	64 (18.5%)
Hepatitis B and Chronic Hepatitis B	3 (0.86%)	1 (0.29%)
HIV infection	3 (0.86%)	3 (0.86%)
Total	196 (56.16%)	206 (59.5%)

*Includes Injection, Intramuscular and Inhaled Heroin and methamphetamine use.
Source: ADMH data set analysis by FDA Medical Reviewer

There were 5 subjects (3 subjects in the single dose and 2 subjects in two dose group) in Trial DUR001-303 who had normal baseline ALT with post baseline elevations of >3 x ULN. All 3 subjects in the single dose group had medical history of chronic hepatitis B or C. Two of them were also IV drug abusers. Among 2 subjects in the two dose group, 1 subject had a history of heavy alcohol intake prior to admission, and was on opiates and acetaminophen treatment in hospital; other subject was on medications that could lead to transaminitis based on package insert (ketoprofen and nimesulide).

Ten subjects had elevated baseline ALT with post baseline elevations of > 3 x ULN (5 subjects each in the single and two dose group). All 5 subjects in the two dose group had medical history of chronic hepatitis C and or IV drug abuse. All 5 subjects in the single dose

group were on drugs that could lead to transaminitis based on package insert information (ketoprofen, nimesulide, metamizole, and or opiates).

Medical Reviewer's Comment: Proportion of patients with underlying liver conditions was similar in both arms and proportion of these patients who had post-baseline ALT elevations of > 3xULN regardless of baseline ALT was also similar in both treatment arms in trial DUR001-303. None of these patients had treatment emergent hepatobiliary adverse events.

7.5.4.2 TEAEs by Baseline Creatinine Clearance (CrCl)

In all phase2/3 dalbavancin trials, at least one TEAE was reported in 41.5% (17/41), 42.0% (172/410), 36.5% (259/710), and 36.6% (465/1270) of patients with baseline CrCl values of <30, 30-59, 60-89, and >90 mL/min, respectively. In the comparator group, TEAE rates were higher, with 42.9% (9/21), 52.0% (117/225), 47.1% (162/344), and 44.8% (272/607) of patients with baseline CrCl values of <30, 30-59, 60-89, and >90 mL/min, respectively. For individual TEAEs, there were no large differences in incidence rates between the baseline CrCl strata.
Similar proportions of subjects had CrCl ≥ 30 ml/min at baseline in single and two dose groups (99% and 98% in single and two dose groups respectively). Subjects with CrCl <30 ml/min at baseline were little lower in single dose compared to two dose group (0.6% vs 2.0% respectively).
Higher proportion of subjects in two dose group with CrCl <30 ml/min experienced TEAEs compared to single dose group (0% vs 44% in single dose and two dose groups respectively). Similar trend was found in subjects with CrCl >30 ml/min, with higher proportions of TEAEs in two dose compared to single dose group (20% vs 40% in single dose and two dose groups respectively). While comparing any dose of dalbavancin with the comparator, rates of TEAEs were higher in comparator arm in both CrCl strata (41.5% vs 42.9% in dalbavancin any dose vs comparator arm with CrCl <30 ml/min; and 37.5% vs 46.8% in dalbavancin any dose vs comparator arm with CrCl >30 ml/min.(**Table 67**)

Table 67 TEAEs by Baseline Creatinine Clearance (CrCl) : Pooled Data from 8 Phase 2/3 Studies

	Dalbavancin Dosage Regimen			
	Single Dose	**Two-Dose**	**Any-Dose**	**Comparator**
	N=349, n(%)	**N=2082, n(%)**	**N=2431**	**N=1197, n(%)**
Baseline CrCl <30	n =2	n =39	n =41	n =21
Any TEAE	0 **(0.0%)**	17 **(43.6)**	17 **(41.5%)**	9 **(42.9)**
Baseline CrCl > 30	n = 347	n = 2043	n = 2390	n=1176
Any TEAE	70 **(20.2)**	826 **(40.4%)**	896 **(37.5%)**	551 **(46.8%)**
Baseline CrCl 30-59	n=51	n=359	N=410	n=225
Any TEAE	11 (21.6)	161 (44.8)	172 (42.0)	117 (52.0)

Baseline CrCl 60-89	N=103	N=607	N=710	N=344
Any TEAE	15 (14.6)	244 (40.2)	259 (36.5)	162 (47.1)
Baseline CrCl ≥90	N=193	N=1077	N=1270	N=607
Any TEAE	44 (22.8)	421 (39.1)	465 (36.6)	272 (44.8)
Cr CL: mL/min; Only TEAEs that occurred for ≥2% of patients in any stratum for dalbavancin (any dose) for baseline CrCl 30-59, 60-89, and ≥90 mL/min. Source: Adapted and modified from Applicant's Table ISS Table 4.2.12				

Medical Reviewer's Comment: Apparently, higher proportion of patients experienced TEAEs in two dose group compared to the single dose group irrespective of baseline CrCl. However the rates of TEAES in patients with CrCl >30 ml/min were higher in the comparator group as compared to the dalbavancin single dose or any dose group. The number of patients with CrCl < 30 ml/min in the dalbavancin single dose group was too small (n=2) to allow meaningful comparison.

7.5.5 Drug-Drug Interactions

A specific clinical drug-drug interaction studies have not been conducted with dalbavancin. In vitro studies using human microsomal enzymes and hepatocytes indicate that dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isozymes so drug-drug interactions between dalbavancin and drugs metabolized by cytochrome P450 are not anticipated.

In clinical trials, the potential for drug-drug interactions was evaluated by examining the proportions of subjects in the phase 2 and 3 trials who had AEs and received concomitant medications of special interest. The concomitant medications of special interest included aztreonam, aminoglycosides, warfarin, and statins. AEs that began on or after the start date of the concomitant medication were considered to have occurred during treatment with the specified concomitant medication. There was no evidence of an increased risk of any TEAE for patients who received aztreonam, aminoglycosides, warfarin or statins in combination with dalbavancin.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Long-term carcinogenicity studies were not conducted with dalbavancin because the drug showed no selective reproductive or developmental toxicity and was non-genotoxic. Also, dalbavancin is not a chronically administered drug. The proposed dosage regimen is single dose infusion of 1500 mg or two-doses of 1000 mg on day 1 followed by 500 mg on day (b) (4)

7.6.2 Human Reproduction and Pregnancy Data

Pregnant subjects were excluded from dalbavancin studies, based on evidence of pregnancy or a possible risk of pregnancy during the period of the clinical studies, there are no controlled data on human pregnancies exposed to dalbavancin.

There were also no studies performed to determine the presence of dalbavancin in human milk. In the 21 clinical studies included in previous NDA 021883 submission in 2013, there was a single case of pregnancy reported in linezolid group and a single positive serum pregnancy test in dalbavancin group in Study VER001-9. Also, there was a report of a single ectopic pregnancy in dalbavancin 1000 mg treatment group in Study DUR001-102. For additional details in these subjects, reader is referred to clinical review by Dr Iarikov. (NDA 021883) There have been no additional pregnancies, nor positive pregnancy tests, in Study DUR001-303.

7.6.3 Pediatrics and Assessment of Effects on Growth

Since dalbavancin will have a limited duration of exposure, adverse effects on human growth are not expected. Data regarding potential effects of dalbavancin in the pediatric population are limited to 2 clinical pharmacology studies (A8841004 and DUR001-106), in which a single dose of dalbavancin was administered to small numbers pediatric patients who were hospitalized with bacterial infections, therefore, the effect of dalbavancin on human growth is not known. Dalbavancin is not proposed for use in the pediatric population in this application.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.6.4.1 Overdose

The effects of dalbavancin overdose have not been studied. However, protocol-specified doses of dalbavancin in some Phase 1 studies (DUR001-104, VER001-2) exceeded the recommended therapeutic doses that were approved for the ABSSSI indication or proposed dose for this application (1500 mg). In addition, 2 subjects in Phase 3 studies (DUR001 302, VER001-8) accidentally received dalbavancin doses that exceeded the recommended therapeutic doses approved for the ABSSSI indication, (**Table 68**). For additional details reader is referred to clinical review of NDA 21883 by Dr Iarikov.

There have been no additional overdoses, relative to those randomly assigned per protocol in Study DUR001-303. Overall, no evident increases in the incidence of AEs were observed in association with increased exposure to dalbavancin.

Table 68 Subjects who received dalbavancin dose greater than 1500 mg				
Study	**Phase**	**Population**	**Dalbavancin dose**	**No of Subjects N=23**
DUR001-104	1	Healthy volunteers	2500mg – 4500 mg in multiple weekly doses	18
VER001-2	1	Healthy volunteers	1600 mg given in multiple doses	3
VER001-8	3	uSSSI	3000 mg as three doses of 1000 mg	1
DUR001-302	3	ABSSSI	3500 mg; 3000 mg on day 1 and 500 mg on day 8	1
Abbreviations: ABSSSI – acute bacterial skin and skin structure infection; uSSSI –uncomplicated skin and skin structures infection;				

7.6.4.2 Drug Abuse

Since glycopeptides, as a drug class, are not known to be associated with abuse potential, the potential for drug abuse with dalbavancin is considered to be low and there is no known chemical or pharmacological basis for abuse potential with dalbavancin. There were no formal studies investigating the dependence potential of dalbavancin in animals or humans have been conducted.
The potential for drug abuse is also considered low due to the IV administration of dalbavancin by healthcare professions in a hospital or clinical setting. No TEAE representing potential abuse of dalbavancin has been identified in any clinical trial performed to evaluate dalbavancin, and no epidemiologic data regarding the potential for abuse of dalbavancin exist. Additionally, no study drug accountability issues were noted during routine monitoring of dalbavancin clinical trial sites.

7.6.4.3 Withdrawal and Rebound

The glycopeptides, as a class, are not known to be associated with withdrawal phenomena. There was no evidence of any withdrawal or rebound effects upon discontinuation of dalbavancin treatment were reported in any of the 8 Phase 2/ 3 studies analyzed in the ISS.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a Periodic Benefit Risk Evaluation Report (PBRER) since the period dalbavancin was marketed for use (for the period of 23 NOV-2014 through 22-MAY-2015), indicating that there was no new safety information to report.
No new safety issues in addition to those described in this review, or in the current prescribing information for DALVANCE® (DALVANCE Package Insert, 2014) have been reported by the Applicant.

7.8 Safety Summary

In summary, the proportions of patients in the safety population who completed the study having been treated with at least one dose of study drug were high and similar across treatment groups. In the single dose group, all 349 patients (100%) in the ITT population received a day 1 dalbavancin dose. In the two dose group, 346/349 patients (99.1%) in the ITT population received a day 1 dalbavancin dose; A total of 326/349 (93.4%) subjects in the two dose group received two doses of study drug. All of the patients who had CrCl <30 mL/min without regular hemodialysis or peritoneal dialysis received appropriately reduced doses of dalbavancin: 2 patients (0.6%) in the single dose group and 7 patients (2.0%) in the two dose group.

The proportions of subjects with preferred terms that may indicate allergic reactions was similar between dalbavancin treatment groups (16/349 (4.6%) vs 13/346 (3.8%) in single dose and two dose groups respectively). No case of anaphylactic reaction or DRESS syndrome was reported in DUR001-303 trial.

Incidence of potential infusion site reactions were slightly lower in the single dose group compared to the two dose group, 4 events in 3 subjects (0.86%) vs. 13 events in 7 subjects (2.0%), respectively.

The incidences of TEAEs were low and similar across study groups. There were total of 115 events in 70 subjects (20%) and 119 events in 69 subjects (19.9%) in the single dose and two dose groups respectively. The most common AEs were nausea (3.4% and 2%), followed by vomiting (1.7% and 1.2%), headache (1.7% and 0.9%), diarrhea (1.1% and 0.6%) and dizziness (1.1% vs 0%) in the single and two dose groups, respectively.

Most TEAEs were mild or moderate; severe TEAEs were observed for ≤2.3% of patients in each treatment group. One patient in each treatment group died during the study; neither death was related to study medication.

The percentages of patients with TEAEs related to study drug were similar across treatment groups (7.2% vs 7.5% in single and two dose groups, respectively). The particular TEAEs most commonly related to study drug were nausea, headache, and vomiting, and the percentages of patients with each were similar across treatment groups. Only 2 patients, both in the two-dose group, had serious TEAEs related to the study drug.

The percentages of patients with TEAEs that led to premature discontinuation from study drug were similar across treatment groups (1.7% and 1.4% in the single and two dose groups, respectively). The only particular TEAE that led to discontinuation for >1 patient within a treatment group was generalized rash (2 patients in the two-dose group).

The mean and median durations of TEAEs were similar when all events were considered together, and when all events related to study drug were considered together. The time to onset of TEAEs was similar between the two treatment groups.

Proportions of patients with underlying liver associated conditions were similar in both single and two-dose arms. None of the patient's ALT elevations were treatment emergent, or met the selected criteria for SAE.

The incidences of subjects with PCS chemistry values, PCSC chemistry values and PCS chemistry values that were also PCSC were low and similar between the treatment groups in DUR001-303 trial.

No obvious safety signal associated with dalbavancin use and hypertension, hypotension, tachycardia or bradycardia is identified based on available data.

Dose limiting toxicity or TEAEs has not been reported in dalbavancin trials.

In conclusion, 1500 mg dose of dalbavancin delivered as a single infusion resulted in safety outcomes similar to the currently approved same total dose given as 1000 mg on day 1 and 500 mg on day 8. There was no incremental increase in the AEs rate when the total dose of 1500 mg is delivered at one time. Given than the same volume is infused over 30 minutes for the initial dose in both regimens, the concentration of dalbavancin in the infusate is higher in patients receiving the 1500 mg dose relative to a 1000 mg dose. However there were less infusion site reactions reported with single dose compared to the two dose group. The single 1500 mg dose of dalbavancin is as safe as the approved two-dose regimen of 1000mg on day 1 followed by 500 mg on day (b) (4)

8 Post market Experience

Dalbavancin is approved as a two-dose regimen (1000 mg day1, followed by 500 mg day (b) (4) for treatment of ABSSSI. Applicant submitted post marketing safety information on July 20, 2015, consisting of spontaneously reported adverse events following the initial NDA approval (23 May 2014) until a data cutoff of 22 May 2015. Although, dalbavancin also received marketing approval in the European Union (EU) on 19 February 2015 and approval in EU-affiliated countries (Iceland, Liechtenstein and Norway), concurrently or shortly thereafter , no marketing of product has occurred in that region as of the 22 May 2015 data cutoff.

No potential safety signal has been identified based on the submitted report. A total of 31 cases reported a total of 67 adverse events (AEs) out of which 40 events were reported as serious adverse events (SAEs).

The most commonly reported AEs were in the SOC Skin and Subcutaneous Tissue Disorders (n=19), and in SOC Gastrointestinal Disorders (n=10). The most commonly reported AEs were hypersensitivity (n=5), and rash and pruritus (each n=4).
The most commonly reported serious adverse drug reaction (SAR) was hypersensitivity (n=4). There were 5 cases of hypersensitivity reported which included relevant co-reported events of angioedema (2), generalized rash (1), throat tightness (1), dyspnea (2), macular rash (2), pruritus (3), swelling face (1), and Urticaria (2). Four of the 5 cases were considered serious. The majority of these cases were confounded by concomitant medications that are known to cause allergic reaction, however the possibility of a causal relationship with dalbavancin cannot be completely ruled out. Allergic reaction and rash are listed for dalbavancin. Serious hypersensitivity (anaphylactic) and skin reactions are included in the WARNINGS AND PRECAUTIONS section of the USPI.

There was a SAE of death received during the reporting period which described a patient of an unknown age and gender who received dalbavancin for an unknown indication and experienced death three days after taking the last dose of the product. This case cannot be adequately assessed due to lack of information.

No reports on pseudomembranous colitis, hepatic disorders, otovestibular toxicity, hematologic effects, use in immunocompromised patients, use in patients with moderate and severe hepatic impairment, use in patients with a CrCl < 30 mL/min receiving hemodialysis, pediatric use, or use in pregnant and lactating women were received during this interval.

Consistent with the current understanding of the safety profile of dalbavancin, the most commonly reported AEs were similar to those seen in the phase2/3 dalbavancin trials. Review of these post-marketing SAEs and AEs does not provide evidence for the emergence of any new safety signal.

9 Appendices

9.1 Literature Review/References

Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation
http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment, October 2013.
htpp://www.fda.gov/downloads/Drugs/…/Guidances/ucm071185.pdf

9.2 Labeling Recommendations

The proposed package insert (PI)submitted with this efficacy supplement is being reviewed by all disciplines. Labeling discussions are ongoing and the recommendations have not been finalized at the time of this review. Some of the key recommendations under consideration by the clinical review team are outlined below:

1. [redacted] However, information on the efficacy of dalbavancin in patients with ABSSSI associated with bacteremia may be included in the Clinical Studies section of the Package Insert.

2. The reviewer disagrees with the Applicant's proposal to remove Warning 5.3 on Hepatic Effects from the PI, which states that more DALVANCE- than comparator-treated subjects with normal baseline transaminase levels had post-baseline alanine aminotransferase (ALT) elevations greater than 3 times the upper limit of normal in Phase 2 and 3 clinical trials. Based upon the review of ALT elevations in dalbavancin trials, hepatocellular injury associated with dalbavancin use cannot be ruled out. Therefore, at the present time we believe that the warning should remain in the package insert.

3. Regarding the changes proposed by the Applicant to the Microbiology subsection of the PI, the review team has made following preliminary recommendations:

   - Proposal to add [redacted] *to the list of clinically important pathogens and to provide its susceptibility interpretive criteria is not acceptable.* [redacted] is not a known pathogen to cause ABSSSI.
   - Regarding the proposal to increase the breakpoint from 0.12 [redacted] for *S. aureus*, *S. pyogenes, S. agalactiae, S. dysgalactiae, S. anginosus group,* and *E. faecalis,* the discussion of the breakpoints is ongoing. At the time this review was written, it was suggested that a breakpoint of 0.25 may be acceptable for all listed micro-organisms.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned for this supplemental NDA.

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/s/

RAMA KAPOOR
12/04/2015

DMITRI IARIKOV
12/04/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

PHARMACOLOGY/TOXICOLOGY REVIEW(S)

Memo to the Division File

NDA 21883 (S-003) Efficacy Supplement, Submitted 7/20/2015

Dalvance™ Powder for Injection Solution

From: Terry J. Miller, Ph.D., Pharmacology/Toxicology Reviewer, DAIP

Through: Wendelyn Schmidt, Pharmacology/Toxicology Supervisor, DAIP

Date: December 2, 2015

Background:

Dalvance® Powder for Injection Solution is a FDA approved product. The Applicant and manufacturer of Dalvance®, Durata Therapeutics, submitted a NDA efficacy supplement (S-003) seeking FDA approval to add a single 1500 mg dose regimen as an alternative to the two-dose regimen of 1000 mg on Day and 500 mg on Day 8. The applicant submitted no new pharmacology/toxicology studies to support the proposed change in dose. No new pharmacology/toxicology information was reviewed for this efficacy supplement. This NDA review will only include a review of the Applicant's proposed changes to the pharmacology/toxicology relevant sections of the product labeling.

Since this NDA Efficacy Supplement (S-003) for NDA 21883 was submitted after the 6/30/2015 deadline for PLLR compliance in labeling, the Sponsor was advised in the 74-day letter to modify the product labeling to ensure compliance with the PLLR Final Rule. Amongst the several other proposed updates to the labeling, the Applicant proposed several changes to the pharmacology/toxicology relevant sections of the labeling ***(Sections 8.1 Pregnancy, 8.2 Lactation,*** (b) (4)

(Note: The previously submitted NDA Labeling Supplement (S-002) for NDA 21883 included labeling revisions to Section 13.1 to include results from an Ames test conducted with Dalbavancin. This revised language does appear in the latest draft of the Applicant's proposed labeling in this NDA Efficacy Supplement (S-003). In the nonclinical review of NDA Labeling Supplement (S-002) by Dr. Terry Miller in DARRTS (11/05/2015), the Ames test and associated changes to Section 13.1 of the product labeling were found acceptable.)

Labeling

The Applicant's Suggested Labeling (From Module 1.14.1.3 Draft Labeling in the NDA submitted on 10/20/2015). The Applicant's proposed labeling changes in the pharmacology/toxicology relevant sections of the labeling can be found in italics and/or strikethrough below. The reviewer's recommended changes are within brackets and bolded below.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy (b) (4)

Risk Summary

There have been no adequate and well-controlled studies with (b) (4) in pregnant women. DALVANCE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No treatment-related malformations or embryo-fetal toxicity were observed in pregnant rats or rabbits at clinically relevant exposures of Dalbavancin. Treatment of pregnant rats with Dalbavancin at 3.5 times the human dose on an exposure basis during early embryonic development and from implantation to the end of lactation resulted in delayed fetal maturation and increased fetal loss, respectively *[see Data].*

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is15 to 20% of clinically recognized pregnancies.

Data

Animal Data

No evidence of embryo or fetal toxicity was found in the rat or rabbit at a dose of 15 mg/kg/day (1.2 and 0.7 times the human dose on an exposure basis, respectively). Delayed fetal maturation was observed in the rat at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis).

In a rat prenatal and postnatal development study, increased embryo lethality and increased offspring deaths during the first week post-partum were observed at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis).

(b) (4)

8.2 *Lactation*

Risk Summary

(b) (4) It is not known whether dalbavancin or its metabolite is excreted in human milk; therefore, caution should be exercised when DALVANCE is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DALVANCE and any potential adverse effects on the breastfed child from DALVANCE or from the underlying maternal condition.

Data

Animal Data

Dalbavancin is excreted in the milk of lactating rats.

(b) (4)

(Reviewer comment: The Applicant's proposed labeling changes in the current NDA Efficacy Supplement (S-003) to sections 8.1, and 8.2 of the product labeling are acceptable. In comments sent in the 74 day-letter, (b) (4)

(b) (4)

Overall Recommendation:
Overall, there are no pharmacology/toxicology issues with the approval of this NDA efficacy supplement to NDA 21883. The applicant submitted no new pharmacology/toxicology studies to support the proposed change in dose and no pharmacology/toxicology information was reviewed for this efficacy supplement. The Applicant's proposed modifications to the labeling for Sections 8.1 and 8.2 are acceptable. (b) (4)

Once the Applicant has agreed these changes, the Applicant's drug labeling should be compliant with PLLR requirements as described in the PLLR Final Rule.

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/s/

TERRY J MILLER
12/30/2015

WENDELYN J SCHMIDT
01/05/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

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 # :	21883/S-003, S/N: 1078
Drug Name:	DALVANCE® (dalbavancin) for Injection
Indication(s):	Treatment of adult patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) caused by susceptible strains of gram-positive bacteria
Applicant:	Durata Therapeutics, Inc.
Stamp Date:	July 20, 2015
PDUFA Goal Date:	January 20, 2016
Reviewer Completion Date:	December 15, 2015
Biometrics Division:	Division of Biometrics IV
Medical Division:	Division of Anti-Infective Products (DAIP)
Documents Reviewed:	NDA 21883, \\Cdsesub1\evsprod\NDA021883\1078
Statistical Reviewer:	Christopher Kadoorie Ph.D.
Concurring Reviewer:	Karen Higgins Sc.D.
Clinical Reviewer:	Rama Kapoor M.D.
Clinical Team Leader:	Dmitri Iarikov M.D., Ph.D.
Project Manager:	Chris Davi M.S.

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1. EXECUTIVE SUMMARY

This submission provides adequate evidence of efficacy to support the approval of DALVANCE 1500mg IV single dose in treating adult patients with ABSSSI. The pivotal Phase 3 trial included in this submission, Trial DUR001-003, met its primary objective by showing the non-inferiority of this single dose regimen of dalbavancin to an approved two-dose regimen of dalbavancin (i.e. 1000mg followed one week later by 500 mg). The primary analysis of this trial showed that clinical responder rates at 48 to 72 hours post-baseline in the ITT population were 284/349 (81.4%) for dalbavancin single dose vs. 294/349 (84.2%) for dalbavancin two doses, a treatment difference of -2.9% (95% CI: -8.5, 2.9). These results supported the non-inferiority of dalbavancin single dose since the lower 95% confidence limit for the treatment difference was -8.5% which exceeded -10%, the minimum allowable limit based on the pre-specified 10% NI margin, **Table 5**.

Key secondary analyses of clinical status at end of treatment (EOT) on Day 14-15 and clinical status at the final visit (FV) on Day 28 also showed similar treatment effects in both arms. Success rates for clinical status at EOT and at FV for dalbavancin single dose versus dalbavancin two doses were 293/349 (84.0%) vs. 296/349 (84.8%), a difference of -0.9% (95% CI: -6.3, 4.6) and 295/349 (84.5%) vs. 297/349 (85.1%), a difference of -0.6% (95% CI: -6.0, 4.8), respectively (**Table 6**). Findings for clinical status at FV also satisfied an additional requirement from the Division aimed at ensuring the sustainability of the treatment effect at 48-72 hours. This requirement stipulated that the lower 95% confidence limit for the treatment difference in clinical status at FV must be -15% or greater (i.e. stay within a 15% threshold) in order for the trial to be considered successful.

In addition to the above primary and secondary analyses, the Reviewer conducted several sensitivity analyses. These analyses showed that primary and secondary analysis results were generally robust across a variety of Reviewer specifications relating to the analysis population, subgroups based on potential confounding variables (e.g. prior/concomitant antibiotic use) and methodologies and criteria used for outcome assessment (e.g. responder/success rates when requiring larger % reductions in lesion area). The Reviewer also conducted exploratory analyses such as analyses of concordance/discordance with reasons for failures or indeterminate assessments at later visits in responders at 48-72 hours. These analyses further supported the robustness of the evidence by showing the sustainability of the treatment effect of dalbavancin single dose at 48-72 hours after baseline to later visits such as EOT and FV.

In summary, there were no major statistical issues identified in this submission. Although the majority of comparisons in Trial 303 tended to be slightly less favorable in the dalbavancin single dose arm, treatment differences were still robust under the assumption of non-inferiority using a 10% NI margin. However, there are still some limitations which should be noted, as discussed in **Section 5.1**. For example, the Reviewer identified a few subgroups where primary and secondary analysis findings could potentially be less favorable to the dalbavancin single

dose arm (e.g. patients meeting systemic inflammatory response syndrome (SIRS) criteria or having fever at baseline), **Table 16**. In addition, lower success rates at EOT and FV were observed in the dalbavancin single dose arm among patients requiring the use of concomitant drug therapies (e.g. aztreonam or metranidazole), **Table 12**. However, the interpretation of such findings may be challenging without the benefit of having a second ABSSSI trial. (b) (4)

[redacted]

2. INTRODUCTION

2.1 Overview

Background

DALVANCE for injection was approved by the Agency on May 23, 2014 for the indication of ABSSSI caused by designated susceptible strains of Gram-positive microorganisms, including MRSA, in adult patients. The approved dosing regimen for dalbavancin is a two dose regimen of 1000 mg followed one week later by 500 mg, each administered over 30 minutes via IV infusion. The approval was based on two Phase 3 clinical trials (Trials DUR001-301 and DUR001-302) that demonstrated non-inferiority (NI) against a comparator regimen of twice-daily vancomycin IV (with option to switch to oral linezolid after 3 days). The selection of the two-dose dalbavancin regimen for these 2 pivotal studies was based on pharmacokinetic (PK) and pharmacodynamic (PD) data from humans, animal models of infection, and in vitro inhibitory and bactericidal activity.

The Applicant is now seeking approval for an alternative dosing regimen for dalbavancin which is a single dose of 1500mg of dalbavancin administered on Day 1. To support approval, this submission includes findings from a single pivotal Phase 3 non-inferiority trial (Trial DUR001-003) which compares a single dose of intravenous dalbavancin 1500 mg to the approved two dose regimen of dalbavancin. This review primarily focuses on the efficacy evaluation of Study DUR001-003, hereafter referred to as Study 003.

Class and Indication

Dalbavancin is a second generation semi-synthetic lipoglycopeptide antibiotic structurally related to teicoplanin. Its mechanism of action involves the interruption of cell wall synthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits. This disruption of the cell wall results in bacterial cell death. Dalbavancin was active against Gram-positive bacteria in in vitro studies. Its potent in vitro activity has been substantiated in various animal models of infection and it possesses a pharmacokinetic (PK) profile which allows once-weekly intravenous (IV) dosing.

Dalbavancin is indicated for the treatment of adult patients with acute bacterial skin and skin

structure infections (ABSSSI), including patients with concurrent bacteremia caused by susceptible strains of the following Gram-positive microorganisms:

- *Staphylococcus aureus (*including *MRSA* strains*)*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus group (*including *S. anginosus, S. intermedius, S. constellatus)*
- *Streptococcus dysgalactiae*
- (b) (4)
- *Enterococcus faecalis*

Applicant's Rationale for Dalbavancin (Single Dose)

The Applicant states that there is continuing emergence of resistance among Gram-positive pathogens worldwide resulting in an increasing medical need for new antibacterial agents with enhanced Gram-positive activity. Recently approved agents for the treatment of SSSIs such as quinopristin/dalfopristin, daptomycin, ceftaroline fosamil and teicoplanin have limitations (e.g. inhibition of hepatic cytochrome P450 3A4 by quinupristin, myelosuppression by linezolid, beta-lactam allergies, and the need for twice daily IV dosing and the requirement for an altered dosing regimen for teicoplanin and vancomycin in renal failure). The Applicant further states that a medicinal agent with clinical efficacy against Gram-positive pathogens, including MRSA, a favorable benefit/risk ratio, and a favorable PK profile would be a valuable addition to the antibacterial armamentarium for the treatment of ABSSSI.

The Applicant also states that there are additional advantages in using the single dose regimen of dalbavancin since the drug can be given only once which is favorable in terms of patient compliance. In addition, there is no need for an oral step-down therapy. Dosing adjustment is not needed except for patients with creatinine clearance less than 30 mL/min who are not on hemodialysis or peritoneal dialysis. For these patients, a dosing guideline has been provided by the Applicant.

History of Product Development

The following is a timeline of some of the notable events in the history of product development for dalbavancin two doses and dalbavancin single dose.

- The dalbavancin NDA 21-883 was 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 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 EOP2 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.

- The SPA-3 clinical protocol for the single dose regimen of dalbavancin was submitted on February 7, 2014.
- SPA-3 Agreement was reached on March 21, 2014 for Trial DUR001-003.
- Dalbavancin dosed 1000mg on Day 1 and 500mg on Day 8 was approved on May 23, 2014.
- The supplemental NDA for the single dose regimen of dalbavancin was submitted on July 20, 2015.

Brief Overview of Trial 303

Table 1 provides a brief overview of the single Phase 3 trial for ABSSSI that was provided in this submission, Trial 303.

Table 1: Overview of Trial 303

Objective	To compare the efficacy and safety of dalbavancin single dose to dalbavancin two dose for the treatment of acute bacterial skin and skin structure infections
Study Design and Type of Control	Phase 3, randomized, double-blind, multi-center, controlled
Indication	ABSSSI with suspected or confirmed Gram positive bacterial pathogens, requiring parenteral therapy
Test Product(s); Dosage Regimen; Route of Administration	**IV dalbavancin single dose**: 1500 mg, or dose adjusted for CrCl on Day 1 **IV dalbavancin two dose**: 1000 mg, or dose adjusted for CrCl on Day 1, 500 mg, or dose-adjusted for CrCl on Day 8
Number of Subjects	598 ITT subjects (349 IV dalbavancin once dose, 349 IV dalbavancin two doses)
Subjects Studied	Adults aged 18–85 with ABSSSI known or suspected to be caused by gram positive bacteria
Duration of Treatment	Multiple dose (10–14 days)
Location	60 sites in North America (US) and Europe (Croatia, Georgia, Estonia, Hungary, Latvia, Russia, Romania, Serbia, South Africa and Ukraine)
Start/Completion Dates	Started: April 18, 2014, Completed March 11, 2015

Source: Reviewer Table

2.2 Data Sources

The Reviewer primarily considered the clinical summary of efficacy, clinical study report and selected datasets which are described below for Trial 303 along with their links. The data formats used in this submission were SDTM and ADAM.

- Clinical Summary of Efficacy : \\Cdsesub1\evsprod\NDA021883\1078\m2\27-clin-sum
- Clinical Study Report: \\Cdsesub1\evsprod\NDA021883\1078\m5\53-clin-stud-rep\535-rep-effic-safety-stud\absssi\5351-stud-rep-contr\dur001-303

- Datasets: \\Cdsesub1\evsprod\NDA021883\1078\m5\datasets\dur001-303\analysis\adam\datasets
  - ADSL- Demographic and Baseline Characteristics
  - ADCM- Concomitant Medications
  - ADABS- Description and Measurements of ABSSSI
  - ADISA- Local signs and symptoms
  - AXEFF- 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 successfully reproduce all major analyses.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

Study Title: "A Phase 3b, Double-Blind, Multicenter, Randomized Study to Compare the Efficacy and Safety of Single Dose Dalbavancin to a Two Dose Regimen of Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infections"

Treatment Arms: Approximately 698 adult patients were to be randomly assigned in a 1:1 ratio to the treatment groups below.

- Patients randomized to the single dose dalbavancin group were to receive a single dose of dalbavancin IV on Day 1, and a dalbavancin-matching placebo IV on Day 8.
- Patients randomized to the two dose dalbavancin group were to receive the first dose of dalbavancin IV on Day 1, and the second dose of dalbavancin IV on Day 8.

The above dosages of dalbavancin may be reduced in patients with low creatinine clearance CrCl at baseline. Among patients with CrCl <30 mL/min who were not receiving regular hemodialysis or peritoneal dialysis, those in the single dose arm received 1000 mg on Day 1 and those in the two-dose arm received 750 mg on Day 1 and 375 mg on Day 8.

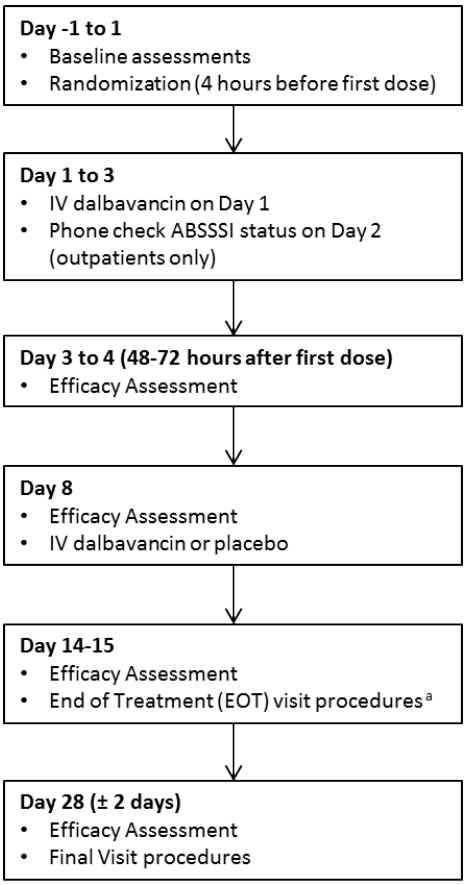
Reviewer Comments: *The sample size of 698 patients was increased from the original sample size of 410 patients due to the results of the planned blinded interim analysis.*

Figure 1 provides a summary of the study visit schedule. Study procedures were to be conducted at Baseline and at a series of 6 timepoints thereafter:

- **Day 1:** Treatment begins; baseline assessments were to be performed within 24 hours before the first dose of study drug, and patients were to be administered the first dose of study drug within 4 hours of randomization.
- **Day 2:** Patients being treated on an outpatient basis were to be contacted by the investigator to check for worsening of the presenting ABSSSI lesion.
- **Day 3-4:** Efficacy assessments were to be performed
- **Day 8:** Patients were to be administered the second dose of study drug;
- **Day 14-15:** This was defined as the End of Treatment (EOT) Visit;
- **Day 28:** This was defined as the Final Visit.

Safety assessments were to be performed at every visit. Patients who discontinued treatment with study drug, for any reason, were encouraged to complete the trial. These patients would at least have a final study visit within 3 calendar days after discontinuation, at which all EOT Visit procedures were to be performed. These patients were also to be requested by the investigator to return for a Final Visit on Day 28; the investigator was required to follow up with the patient through Day 28 regarding any unresolved adverse events whether or not this Final Visit occurred.

Figure 1: Overall Study Design



[a] If treatment was prematurely discontinued, the EOT visit was scheduled for within 3 days of discontinuation.

Source: Partially Adapted from Applicant Figure 1 in CSR

Inclusion Criteria:

The Reviewer's summary of the key inclusion criteria for enrollment into the study are provided below:

1. Male or female patients, 18-85 years of age providing informed consent.
2. ABSSSI (suspected or confirmed to be caused by Gram-positive bacteria) defined as an infection (major cutaneous abscess, surgical site or traumatic wound infection, or cellulitis) 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 is accompanied by erythema, edema and/or induration which:
        i. required surgical incision and drainage (I&D), and
        ii. was associated with cellulitis such that the total affected area involved at least 75 cm^2 of erythema, and
        iii. Margin of erythema that was ≥5 cm from the rim of induration or edema that defines the border of the abscess in all directions, or,
        iv. 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 is associated with cellulitis such that:
        i. the total affected area involved at least 75 cm^2 of erythema, and
        ii. was defined by a margin of erythema in at least one direction that was ≥5 cm from the edge of the wound, or
        iii. 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 one 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:
        i. was associated with erythema that involved at least 75 cm^2 of surface area, or
        ii. alternatively, cellulitis of the central face that was associated with an affected area of at least 50 cm^2
3. In addition to the requirement for erythema, all patients were required to have at least 2 of the following signs of ABSSSI:
    a. Purulent drainage/discharge
    b. Fluctuance
    c. Heat/localized warmth
    d. Tenderness to palpation
    e. Swelling/induration
4. All patients were required to present with at least ONE of the following systemic signs of infection:

a. An elevated body temperature ≥38°C/100.4°F as measured by the patient/caregiver or investigator within 24 hours of baseline;
b. White blood cell count >12,000 cells/mm3;
c. A manually performed white blood differential count with ≥10% band forms, regardless of peripheral white blood cell count.

c. A manually performed white blood differential count with ≥10% band forms, regardless of peripheral white blood cell count.

5. All patients were required to be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Randomization:

Approximately 698 patients were to be randomized in a 1:1 allocation ratio to either the single dose dalbavancin group or the two-dose dalbavancin group, using block randomization (block size 4). The initial determination of the sample size was 410 patients, but was increased during the study based on results from a blinded interim analysis. Randomization was conducted according to a randomization schedule generated by an Interactive Web Randomization System (IWRS). Randomization was stratified by geographic region, infection type (major abscess, cellulitis, or traumatic wound/surgical site infection), and prior use of antibiotics for ABSSSI.

Analysis Populations:

The following are analysis populations as defined by the Applicant. Note that Reviewer analyses primarily considered the ITT and micro ITT populations.

ITT population- All randomized patients regardless of whether or not they received study drug (a patient was considered randomized beginning at the moment the pharmacist or designee received the treatment assignment from the IWRS). Inclusion in the ITT population was determined programmatically based on eCRF data.

Modified ITT/Safety Population- All patients in the ITT population who received at least 1 (active) dose of dalbavancin are included in the mITT population that also serves as the safety population. Inclusion in this population was determined programmatically based on eCRF data.

Clinically Evaluable Populations- Two different CE populations are defined based on the timing of the outcome assessment to be evaluated: CE-EOT and CE-Final Visit. Any patient who met all of the following criteria is included in the CE population for the respective visit:

- Fulfilled patient selection criteria such that the evaluation of Clinical Status was not confounded:
- Received dalbavancin as randomized, specifically 1 dose for patients in the single-dose treatment group or 2 doses for patients in the two-dose treatment group.

- Received for a non-ABSSSI indication no more than one dose of another systemic antibacterial therapy that has documented activity against the causative organism, during the period from first dose of study drug to EOT (for the CE-EOT population) or Final Visit (for the CE-Final Visit population). Patients who received a new, non-study systemic antibacterial drug (other than aztreonam or metronidazole) for the treatment of ABSSSI were to be considered 'evaluable failures' and therefore included in the CE population for the respective visit.
- Had an outcome assessment at which Clinical Status could be evaluated as follows:

  - The CE-EOT population includes all patients with an assessment in the time window from Study Day 12 through Study Day 18, plus those who had assessments within 3 days of premature discontinuation from study drug and those who were considered clinical failures and received a concomitant antibiotic for worsening of the primary ABSSSI lesion prior to Study Day 12.

  - The CE-Final Visit population includes all patients with an assessment in the time window from Study Day 26 through Study Day 30 plus those who were considered clinical failures at EOT and received a concomitant antibiotic for worsening of the primary ABSSSI lesion.
- Received appropriate adjunctive antibacterial coverage if the patient had a culture-documented mixed ABSSSI (one or more Gram-positive pathogens with one or more Gram-negative aerobic or anaerobic organisms).

Micro-ITT- The micro-ITT population includes all patients in the ITT population who had at least 1 Gram-positive pathogen isolated at Baseline, from either a blood culture or culture of a microbiological sample obtained from the presenting ABSSSI lesion

Micro-Modified ITT- The micro-mITT population includes all patients in the mITT population who also met criteria to be included in the micro-ITT population

Micro Evaluable Populations- Each ME population included only patients who qualified to be included in both the micro-ITT population and the respective CE population

Reviewer Comments: *The evaluable and micro evaluable populations were considered to be limited by potential biases which can occur from patient exclusions occurring post-baseline.*

Sample Size Determination:

The study is designed to determine whether the single dose dalbavancin regimen is non-inferior to the two dose regimen when evaluated for clinical response at 48-72 hours after initiation of study drug in the ITT population.

Initially, the proposed sample size was 205 patients per treatment group based on the method of Farrington and Manning[1], assuming a non-inferiority margin of -10%, power of 90%, a one-sided alpha level of 0.025, and a 90% treatment response rate. The expected 90% treatment response rate is estimated from 2 large and recently completed randomized controlled trials of dalbavancin (Studies DUR001-301 and DUR001-302) in a similar patient

population. In both of these previous studies, the measured response rate in the ITT population, when responders were defined as having lesion area reduced ≥20% at 48-72 hours after the initiation of study drug, was approximately 90% (i.e. 89.9% in Study DUR001-301 and 87.6% in Study DUR001-302).

To test the assumption of a 90% response rate, an interim analysis was performed when approximately 60% of the planned 410 patients had been enrolled. In this blinded interim analysis, the aggregate responder rate for Clinical Response at Day 3-4 was <90%, and a sample size increase to 698 randomized patients (i.e. 349 patients per treatment group) was recommended by an independent, blinded Data Monitoring Committee in order to maintain adequate power for NI testing.

Reviewer Comments: *Since the sample size increase was based on a blinded interim analysis with no chance of stopping early for efficacy, it does not affect the overall type I error rate of the study.*

Endpoints:

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

A patient will be programmatically defined as a clinical responder if the following criteria are met:

- The patient is alive and has received no rescue therapy for ABSSSI prior to the 48-72 hour infection site assessment (if an antibiotic has been given for another reason, the patient will not be considered a non-responder for this reason); and
- Examination of the patient's ABSSSI lesion demonstrates a decrease of ≥20% in lesion area (calculated as the longest length multiplied by the longest perpendicular width) relative to the baseline measurement.

Patients who did not meet this definition are considered non-responders.

Lesion area is defined as length x width and lesion size is defined as length or width. The baseline lesion measurement is defined as the measurement taken closest to but prior to the first dose of study drug. If multiple lesions measurements are taken within 48-72 hours after the first dose of study drug, the latest lesion measurement will be used.

Key Secondary Efficacy Outcome Measures: Key secondary outcome measures are clinical status at the EOT visit (Day 14-15 [window Day 12 - Day 18]) and clinical status at the final visit (Day 28 [window ±2 days]).

A patient will be programmatically defined as a clinical success based on the following:

- For evaluation at the EOT visit, the patient's lesion area must be decreased by ≥80% from baseline, and for evaluation at the Final Visit, the patient's lesion area must be decreased by ≥90% from baseline;

- The patient's temperature is ≤37.6°C (by any measurement method);
- Local signs of tenderness to palpation and swelling/induration are no worse than mild;
- For evaluation at the EOT visit, local signs of fluctuance and localized heat/warmth must be improved from baseline and no worse than mild, and for evaluation at the Final Visit, local signs of fluctuance and localized heat/warmth must be absent;
- For patients with a wound infection the severity of purulent drainage is improved and no worse than mild relative to baseline.

A patient was defined as a clinical failure if at least one of the following criteria is met:

- The patient's lesion area, as defined by erythema, is not decreased from baseline by ≥80% for evaluation at the EOT visit, or by ≥90% for evaluation at the Final Visit; or
- For evaluation at the EOT visit, local signs of fluctuance and localized heat/warmth are not improved from baseline or worse than mild, and for evaluation at the Final Visit, local signs of fluctuance and localized heat/warmth are present; or
- Local signs of tenderness to palpation and swelling/induration are worse than mild; or
- For patients with a wound infection the severity of purulent drainage is the same as or worse than baseline, or is worse than mild; or
- The patient had a temperature of >37.6°C (by any measurement method) at the visit; or
- The patient received a new non-study systemic antibacterial treatment for the primary ABSSSI lesion 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
- The patient received study therapy for the ABSSSI beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy is needed for treatment of the ABSSSI under study.

A patient was defined as having indeterminate clinical status if any of the data needed to determine clinical success or clinical failure, as defined above, were missing. By definition, patients with indeterminate clinical status are included in the denominator for evaluations in the ITT population, and are counted as clinical failures.

Prior and Concomitant Therapy:

Prior Medications

Exclusion criteria related to the use of medications prior to enrollment are listed below:

- Patients with a contra-indication to the administration of dalbavancin, such as, hypersensitivity to any of the glycopeptide agents.
- Participation in another study of an investigational drug or device within 30 days prior to enrollment.
- Receipt of a systemically or topically administered antibiotic with a Gram-positive spectrum that achieves therapeutic concentrations in the serum or at the site of the ABSSSI within 14 days prior to randomization. An exception is allowed for patients receiving a single dose of a short-acting (half-life ≤12 hours) antibacterial drug prior to randomization. However, no more than 25% of patients were to have

received prior antibiotic therapy for the presenting ABSSSI, based on medical history available at the time of randomization.

- Patients receiving oral steroids >20 mg prednisolone per day (or equivalent) or receiving immunosuppressant drugs after organ transplantation.

Concomitant Therapies

In Trial 303, any medication taken by the patient during the study, other than study drug, was to be considered concomitant medication. The use of any investigational drug other than dalbavancin was prohibited. The use of other (non-antibacterial) medications was to be limited to those essential for the care of the patient.

Concomitant treatment with systemic and topical antibacterial medications was prohibited during the study, up to the EOT visit, with the following exceptions:

- Vancomycin oral 125 mg or 250 mg every 6 hours was allowed in both treatment groups for the treatment of Clostridium difficile infection,
- Metronidazole IV or oral 500 mg every 8 hours was allowed in both treatment groups for the treatment of Clostridium difficile infection
- Other antibacterial medications that do not achieve therapeutic levels in the serum (eg, nitrofurantoin) or at the site of the ABSSSI lesion could have been considered

Adjunctive treatment for ABSSSI with systemic and topical antibacterial medications was prohibited during the study, up to the EOT visit, with the following exceptions:

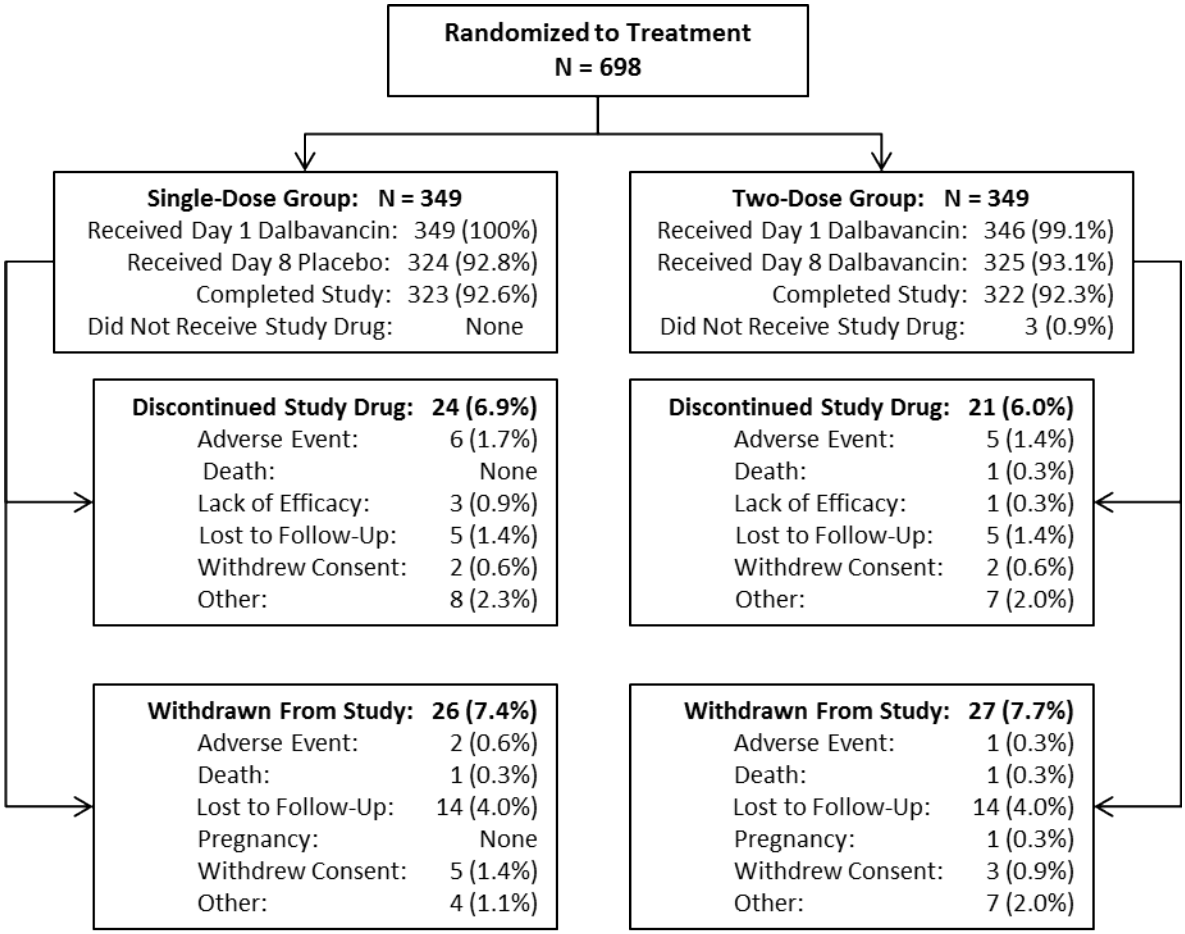
- Metronidazole IV or oral 500 mg every 8 hours was allowed in both treatment groups for infection with suspected anaerobic pathogens.
- Aztreonam was allowed in both treatment groups for the treatment of ABSSSI caused by Gram-negative bacteria, and was the only systemic antibacterial medication allowed for empiric treatment based on information available at the time of randomization. Empiric treatment with aztreonam post-randomization was not permitted, but use of aztreonam to treat an infection with a Gram-negative bacterial species confirmed by culture was acceptable at any time during the study.

3.2.2 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

In Trial 303, patient disposition was similar across treatment groups in the ITT population (**Figure 2**). There were 698 patients randomly assigned to treatment (349 patients and 349 patients in the dalbavancin single dose and dalbavancin two doses groups), and 645 patients (92.4%) completed the study (323 patients and 322 patients, respectively). Subjects were enrolled from 60 sites in North America (US) and Europe (Croatia, Georgia, Estonia, Hungary, Latvia, Russia, Romania, Serbia, South Africa and Ukraine).

Figure 2: Disposition of Patients (ITT)



Source: Applicant Figure 4 in CSR

Reviewer Comments: *There were no notable differences between the treatment arms with respect to discontinuations from study drug or study withdrawals.*

In **Table 2**, demographic and baseline characteristics were generally similar between both treatments (dalbavancin single dose vs. dalbavancin two doses). No substantial differences were noted between treatment arms with respect to age, gender, ethnicity, race, region, infection type.

Table 2: Demographics and Baseline Characteristics (ITT)

	Trial 303		
	Dalbavancin 1 Dose (n=349) n (%)	**Dalbavancin 2 Doses (n=349) n (%)**	**Total (n=698)**
Age, n (%)			
Mean (Std. dev.)	48.0 (14.8)	48.3 (14.7)	48.2 (14.8)
Median (Min, Max)	49 (18, 85)	50 (19, 84)	50 (18, 85)

Gender, n (%)			
Female	145 (41.5)	146 (41.8)	291 (41.7)
Male	204 (58.5)	203 (58.2)	407 (58.3)
Ethnicity, n (%)			
Hispanic or Latino	51 (14.6)	60 (17.2)	111 (15.9)
Not Hispanic or Latino	289 (82.8)	283 (81.1)	572 (81.9)
Unknown/ Other	9 (2.6)	6 (1.7)	15 (2.1)
Race, n (%)			
White	312 (89.4)	311 (89.1)	623 (89.3)
African American	28 (8.0)	31 (8.9)	59 (8.5)
Other	9 (2.6)	7 (2.0)	16 (2.3)
Region, n (%)			
North America	158 (45.3)	160 (45.8)	318 (45.6)
Rest of World	191 (54.7)	189 (54.2)	380 (54.4)
Infection Type, n (%)			
Cellulitis	167 (47.9)	166 (47.6)	333 (47.7)
Major abscess	86 (24.6)	89 (25.5)	175(25.1)
Traumatic wound/ surgical site infection	96 (27.5)	94 (26.9)	190 (27.2)

Source: Reviewer Table

In **Table 3**, disease severity characteristics at baseline were generally similar between treatments (dalbavancin single dose vs. dalbavancin two doses).

Table 3: Disease Severity at Baseline for Patients Included in ITT

Disease Severity **Subjects With:**	**Study 303**		
	Dalbavancin 1 dose (n=349)	**Dalbavancin 2 doses (n=349)**	**Total (n=698)**
Pathogen at Baseline, n (%)			
Pathogen	210 (60.2)	220 (63.0)	430 (61.6)
No Pathogen	139 (39.8)	129 (37.0)	268 (38.4)
Medical history, n (%)			
Age ≥ 65 yrs	41 (11.7)	49 (14.0)	90 (12.9)
Diabetes mellitus	19 (5.4)	21(6.0)	40 (5.7)
Renal function (CrCl in mL/min)	n=349	n=347	n=696
< 30	2 (0.6)	7 (2.0)	9 (1.3)
≥ 30	347 (99.4)	340 (98.0)	687 (98.7)
Signs and symptoms (s/s), n (%)			
Fever	290 (83.1)	283 (81.6)	573 (82.1)
WBC Count > 12,000/mm^3	132/348 (37.9)	126/342 (36.8)	258/690 (37.4)
Bacteremia	12 (3.4)	10 (2.9)	22 (3.2)

Source: Reviewer Table

Table 4 compares the primary site infection areas (cm^2) at baseline, both overall and by type of infection, between the treatment arms. Infection areas based on the median were similar between the arms. Mean ± SD (median) infection areas were 497±599 (296) cm^2 for dalbavancin single dose vs. 449 ±434 (293) cm^2 for dalbavancin two doses. Treatments were found to be appropriately balanced with respect in infection areas both overall and by disease type with no significant treatment differences identified.

Reviewer Comments: *Since infection area measurements were highly positively skewed, median area measurements were considered to be more informative for comparative purposes.*

Table 4: Primary Infection Site Area at Baseline, Overall and by Infection Type (ITT)

Infection Area (cm^2)	Study 303	
	Dalbavancin 1 Dose (n=349)	**Dalbavancin 2 Doses (n=349)**
Overall		
	n=349	n=346
Mean ± SD	497±599 cm^2	449±434 cm^2
Median (range)	296 (56, 4325)	293 (77, 2688)
Subjects with Cellulitis		
	n=165	n=165
Mean ± SD	657±771	573±550
Median (range)	376 (61,4235)	345 (80, 2668)
Subjects with Major Abscesses		
	n=88	n=89
Mean ± SD	349±362	298±155
Median (range)	270 (56, 3120)	261 (110,850)
Subjects with wound infection		
	n=96	n=92
Mean ± SD	321±263	373±300
Median (range)	257 (77, 1944)	278 (77, 1568)

Source: Reviewer Table

3.2.3 Statistical Methodologies

3.2.3.1 Statistical Methodologies (Applicant)

The primary efficacy analysis was performed in 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 not adjusted for baseline covariates.

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 one-dose treatment group, p_2 was the rate of the primary efficacy outcome measure in dalavancin two-dose 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 one-dose treatment minus dalbavancin two-dose 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 one-dose to dalbavancin two-dose was concluded.

The 2-sided 95% CI for non-inferiority testing based on the difference of clinical response rates at 48 to 72 hours was computed using the method proposed by Miettinen and Nurminen without stratification[2]. This 95% CI is computed using Cochran-Mantel-Haenszel stratum weights, without adjustments for the stratification factors employed in randomization (i.e. geographic region, infection type, and prior use of antibiotics).

Reviewer Comments: *Estimation of the 95% confidence intervals in the primary analysis for the treatment difference based on the Miettinin and Nurminen (MN) approach (unadjusted for covariates) is considered acceptable.*

NI Margin (Delta) Selection: A 10% non-inferiority margin was used to determine treatment efficacy in the primary analysis of Study 303.

Reviewer Comments: *A 10% NI margin is justified in the Agency's current ABSSSI NI guidance.[5] This justification is based on two papers published by Snodgrass in 1937[3,4]. It should also be noted that a 10% NI margin was agreed upon with the Agency during the review of this SPA.*

Interim Analyses: A blinded interim analysis with possible sample size re-estimation was performed when approximately 60% of the planned 410 patients had been enrolled. In this interim analysis, the aggregate responder rate for Clinical Response at Day 3-4 (ie, both treatment groups considered together) was <90%, and a sample size increase to 698 randomized patients (ie, 349 patients per treatment group) was recommended by an independent, blinded Data Monitoring Committee.

Reviewer Comments: *The expected 90% treatment response rate is estimated from 2 large and recently completed randomized controlled trials of dalbavancin (Trials 301 and 302) evaluating the same endpoint in a similar patient population. The Reviewer considers this assumption to be reasonable, however a substantially smaller overall treatment response rate was observed in Study 303 (i.e. ~ 82.8%).*

Missing Data: For clinical response, missing data will be handled as follows:

- For the primary outcome measure (clinical response at 48-72 hours), the patient will be considered to have missing data if there is no lesion measurement at baseline and/or in the 48-72 hour (post first dose of study drug) time period. Patients with missing lesion data will be defined as a non-responder for the primary analysis (ITT analysis).

Reviewer Comments: *There were 3 patients in the two dose arm who were untreated and had no lesion measurement at baseline and/or in the 48-72 hour (post first dose of study drug) time period.*

- For the secondary outcome measure (clinical status at EOT and Final Visit), patients will be defined as indeterminate if any data needed to determine whether a patient is success or failure are missing. For example, if the assessment of the local signs was not completed at EOT, for any reason, the patient will be considered to have an indeterminate response. By definition, patients with an indeterminate response are included in the denominator for analyses in the ITT population and are considered failures, and such patients will be excluded for analysis in CE population.

Multiple Comparisons Adjustment: In the Applicant's primary hypotheses, only one statistical hypothesis is tested. The Applicant also specified clinical status at EOT and clinical status at FV as secondary endpoints of interest which were analyzed descriptively. Therefore multiplicity adjustments to control for inflation of the type I error rate in testing the primary endpoint or secondary endpoints was not needed.

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

3.2.3.2 Statistical Methodologies (Reviewer Analyses)

Reviewer primary and secondary analyses used the same approach as the Applicant for testing the primary and secondary hypotheses. Reviewer analyses also estimated the 95% confidence limit of the treatment difference ('dalbavancin single dose' minus 'dalbavancin two doses') using the same unstratified MN approach. Findings from Applicant and Reviewer analyses for primary and secondary analyses were identical.

To further assess the robustness of the evidence of efficacy, the Reviewer also conducted various sensitivity/exploratory analyses which included the following:

- Responder/success rates based on various analysis populations
- Responder/success rates in micro-ITT, overall and by baseline pathogen
- Analyses of concordance/discordance
- Analyses of prior antibiotic use
- Responder/success rates by various subgroups
- Responder/success rates when requiring larger reductions in lesion area
- Reasons for failure/indeterminates
- Time to percent reduction in lesion area
- Analyses of concomitant drug therapies

- Analyses of concomitant non-drug therapies
- Success rates based on investigator assessments
- Absence rates of all local signs

Reviewer Comments: *In addition to the above efficacy analyses, the Reviewer also conducted various safety analyses as described in* ***Section 3.3****.*

3.2.4 Efficacy Results and Conclusions

3.2.4.1 Results of Applicant's Primary and Secondary Analysis

In the Applicant's primary analysis conducted in the ITT population, responder rates at 48-72 hours were compared between dalbavancin single dose and the comparator, dalbavancin two doses, using a 10% NI margin. The Applicant also pre-specified a secondary analysis based on clinical status at EOT and clinical status at FV.

Overall, the treatment difference in the primary analysis based on the ITT population was less favorable in the dalbavancin single dose arm at -2.9% (95% CI: -8.5%, 2.8%). **Table 5** shows that the proportion of patients who were clinical successes at 48-72 hours was 284/349 (81.4%) in the single dose arm compared to 294/349 (84.2%), a treatment difference (single dose – two doses) of -2.9% (95% CI: -8.5%, 2.8%). However, since the lower limit of the 95% confidence interval for the treatment difference was -8.5% which exceeded -10%, the minimum limit under the pre-specified 10% NI margin, these findings were supportive of the non-inferiority of dalbavancin single dose to dalbavancin two doses.

Table 5: Responder Rates at 48-72 hours (Applicant Primary Analysis)

	Study 303		
Analysis Population	**Dalbavancin 1 Dose (n=349)** n (%)	**Dalbavancin 2 doses (n=349)** n (%)	**Treatment Difference (95% CI)**
ITT	284 (81.4)	294 (84.2)	-2.9 (-8.5, 2.8)

Source: Reviewer Table

Findings for the Applicant's key secondary analyses of clinical status at EOT and FV were consistent with primary analysis findings. **Table 6** shows that the proportion of patients who were clinical successes at EOT and FV was slightly lower in the single dose arm compared to the two dose arm. The treatment difference (single dose – two doses) was -0.9% (95% CI: -6.3%, 4.6%) at EOT and -0.6% (95% CI: -6.0, 4.8) at FV.

Reviewer Comments: *During the design stage, the Agency expressed concerns regarding the potential lack of sustainability of the treatment effect of dalbavancin single dose beyond 48-72 hours. Furthermore, evidence of an NI margin may not be clear beyond 48-72 hours (e.g. at EOT or FV). Although there were limitations with defining an appropriate NI margin at later endpoints, the Agency still wanted to pre-specify some 'win criteria' with respect to*

comparisons at later endpoints. The Agency placed a requirement on the lower limit of the 95% CI for the treatment difference at FV which had to be no less than -15% (i.e. meet a 15% threshold at FV). Based on the lower 95% confidence limit of -6.0%, findings for clinical status at FV did support sustainability of the clinical response in the primary analysis.

Table 6: Clinical Success Rates at EOT and FV (ITT), Applicant Secondary Analysis

Study 303	**Dalbavancin 1 dose (n=349)** n (%)	**Dalbavancin 2 doses (n=349)** n (%)	**Treatment Difference (95% CI)**
Clinical Success at EOT	293 (84.0)	296 (84.8)	-0.9 (-6.3, 4.6)
Clinical Success at FV	295 (84.5)	297 (85.1)	-0.6 (-6.0, 4.8)

Source: Reviewer Table

Reviewer Comments: *As noted above, Reviewer primary and key secondary analyses were identical to those of the Applicant.*

Table 7 shows the reasons for failure at EOT and Final Visit (FV) among all patients. Patients in each study arm are failing for mostly similar reasons at both the EOT and FV assessments. However, a greater proportion of patients in the dalbavancin two-dose arm failed due to not meeting the required % reduction in lesion area at EOT and at FV.

Table 7: Reasons for Failure at EOT/FV

All Failures (Clinical Failures & Indeterminates at EOT/FV)	Dalbavacin 1 Dose N=349	Dalbavancin 2 Doses N=349	Dalbavacin 1 Dose N=349	Dalbavancin 2 Doses N=349
	At EOT		At FV	
All Failures	**56 (16.0)**	**53 (15.2)**	**54 (15.5)**	**52 (14.9)**
Indeterminates	**14 (4.0%)**	**17 (4.9%)**	**26 (7.4%)**	**27 (7.7%)**
No EOT/FV visit, missing all measurement data	14 (4.0%)	17 (4.9%)	24 (6.9%)	24 (6.9%)
Have EOT/FV visit, but Data are Missing	0	0	2 (0.6%)	3 (0.9%)
Clinical Failures	**42 (12.0%)**	**36 (10.3)**	**28 (8.0)**	**25 (7.2)**
Lesion size at EOT/FV did not decrease from baseline ≥ 80% (EOT) or ≥ 90% (FV)	31 (8.9%)	24 (6.9%)	15 (4.3%)	9 (2.6%)
Temperature at EOT/FV >37.6C	1 (0.3%)	2 (0.6%)	1 (0.3%)	0
Local sign of heat/warmth and fluctuance not improved or worse than mild (EOT) or not resolved (FV)	4 (1.1%)	5 (1.4%)	3 (0.9%)	3 (0.9%)
Local sign of tenderness and swelling worse than mild	9 (2.6%)	7 (2.0%)	0	2 (0.6%)
Purulent Drainage is same/worse from baseline or worse than mild (wound infections only)	2 (0.6%)	3 (0.9%)	1 (0.3%)	0
Received non-study systemic antibacterial for ABSSSI	9 (2.6%)	6 (1.7%)	11 (3.2%)	12 (3.4%)
Death	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)

Source: Reviewer Table

Reviewer Comments: *While reasons for failure were mostly similar when comparing dalbavancin single dose vs. dalbavancin two doses at EOT and FV, reasons for failure were*

not similar when comparing the EOT vs. FV assessments among all patients. Patients at FV failed more often as a result of missing data or receiving non-study systemic antibacterials while patients at EOT failed more often due to lesion size not decreasing enough or local signs of infection or fever not resolving.

3.2.4.2 Additional Reviewer Analyses

Analysis of Responder Rates at Day 3-4 in the Modified ITT (All-Treated) Population

The Reviewer considers the modified ITT (all-treated) population as an important population to consider in conjunction with the ITT population especially if there is a treatment imbalance between the arms. In Study 303, there was a mild imbalance with all three of the untreated patients originating from the dalbavancin (two dose arm). **Table 8** considers the modified ITT (all-treated) population where these three patients are excluded. Such an exclusion results in comparisons of dalbavancin single dose that are slightly less favorable than in the primary analysis. Comparing **Table 8** (below) with **Table 5** (above) shows that the lower confidence limit shifts from -8.5% to -9.2%, but still exceeds the -10% limit required for demonstrating non-inferiority.

Table 8: Responder Rates at 48-72 hours, Modified ITT (All-Treated) Population

	Study 303		
Analysis Population	**Dalbavancin 1 Dose (n=349)** n (%)	**Dalbavancin 2 doses (n=349)** n (%)	**Treatment Difference (95% CI)**
Modified ITT	284 (81.4)	294 (85.0)	-3.6 (-9.2, 2.0)

Source: Reviewer Table

Micro-ITT Results Overall and by Pathogen

Micro-ITT Results Overall

Table 9 shows overall responder and success rates in the Micro-ITT population. Overall, there were no major differences between the treatments.

Table 9: Responder/Success Rates in Micro-ITT Population

Study 303	**Dalbavancin 1 dose (n=210)** n (%)	**Dalbavancin 2 doses (n=220)** n (%)	**Treatment Difference (95% CI)**
Responder at Day 3-4	184 (87.6)	191 (86.8)	0.8 (-5.7, 7.2)

Clinical Success at EOT	182 (86.7)	198 (90.0)	-3.3 (-9.6, 2.8)
Clinical Successs at FV	183 (87.1)	194 (88.2)	-1.0 (-7.4, 5.3)

Source: Reviewer Table

Micro-ITT Results by Pathogen

Table 10 shows responder rates at 48-72 hours and clinical success rates at EOT and FV by baseline pathogen among those patients included in the micro-ITT population. Overall, comparisons were generally similar between the treatment arms. However, a higher responder rate was observed among patients with MRSA who received dalbavancin single dose vs. dalbavancin two dose at 31/36 (86.1%) vs. 48/61 (78.7%).

Considering success rates at EOT/FV, there were no major differences between the arms. However, rates at EOT and at FV (to a lesser extent) tended to favor the dalbavancin single dose arm for *S.pyogenes* and the dalbavancin two-dose arm for *S.aureus.* However, findings for *S.pyogenes* were limited by the small numbers, especially in the single dose arm. Findings were also very limited for *S.agalactiae, S.dysgalactiae, E.faecalis* due the small numbers.

Table 10: Clinical Success/Responder Rates by Baseline Pathogen (Micro-ITT)

	Study 303	
Pathogen	**Dalbavancin 1 dose (n=210) n/N (%)**	**Dalbavancin 2 doses (n=220) n/N (%)**
Responder Rates at Day 3-4		
S.aureus	123/139 (88.5)	133/156 (85.3)
MRSA	31/36 (86.1)	48/61 (78.7)
MSSA	92/103 (89.3)	86/96 (89.6)
S.agalactiae	6/6 (100)	4/6 (66.7)
S.anginosus group	31/33 (93.9)	19/19 (100)
S.dysgalactiae	4/4 (100)	3/3 (100)
S.pyogenes	14/14 (100)	18/22 (81.8)
E.faecalis	4/4 (100)	8/10 (80.0)
Clinical Success Rates at EOT		
S.aureus	122/139 (87.8)	145/156 (91.7)
MRSA	30/36 (83.3)	53/61 (86.9)
MSSA	92/103 (89.3)	91/96 (94.8)
S.agalactiae	5/6 (83.3)	5/6 (83.3)
S.anginosus group	27/33 (81.8)	17/19 (89.5)
S.dysgalactiae	4 / 4 (100)	3 / 3 (100)
S.pyogenes	13/14 (92.9)	18/22 (81.8)
E.faecalis	4 / 4 (100)	10 / 10 (100)
Clinical Success Rates at FV		
S.aureus	124/139 (89.2)	140/156 (89.7)
MRSA	31/36 (86.1)	55/61 (90.2)

MSSA	93/103 (90.3)	86/96 (89.6)
S.agalactiae	5/6 (83.3)	5/6 (83.3)
S.anginosus group	29/33 (87.9)	17/19 (89.5)
S.dysgalactiae	4 / 4 (100.0%)	3 / 3 (100)
S.pyogenes	13/14 (92.9)	19/22 (86.4)
E.faecalis	4 / 4 (100)	9 / 10 (90.0)

Source: Reviewer Table

Analyses of Concordance/Discordance

Table 11 compares treatments based on clinical success at EOT and FV separately for responders and nonresponders at 48-72 hours. The 'Responders (48-72 hrs)'columns of this table compare the sustainability of the treatment benefit at 48-72 hours through EOT and FV. The 'Non-responders (48-72 hrs)' columns of this table compares the continued effect of the treatment through EOT and FV among patients who failed to respond at 48-72 hours.

Overall, responders at 48-72 hours across both arms had substantially higher clinical success rates at EOT in comparison to non-responders. Among patients in the dalbavancin single dose, responders at 48-72 hours had clinical success rates of 90.1% at EOT and 89.4% at FV while non-responders had success rates of 49.3% and 63.1%, respectively. Similar differences were observed in the dalbavancin two dose arm. Among responders, clinical success rates at EOT and FV were similar for the dalbavancin single dose and two dose arms at 90.1% vs. 90.5% and 89.4% vs. 89.1%, respectively. Among non-responders, there were no major treatment differences. Although clinical success rates at EOT were slightly lower in the dalbavancin single arm at 49.3% vs. 54.5%, similar differences were not observed at FV.

Reviewer Comments: *A comparison of the clinical failure rates among responders and non-responders shows that non-response at 48-72 hours is strong predictor of clinical failure at later visits. This also supports the validity of the primary endpoint of clinical response at 48-72 hours.*

Table 11: Concordance/Discordance Analysis - Responder/Non-Responders at 48-72 hours with Clinical Success/Failure at EOT and FV (ITT)

Trial 303: Responder rates n (%)	Dalbavacin 1 Dose n (%)	Dalbavancin 2 Doses n (%)	Dalbavacin 1 Dose n (%)	Dalbavancin 2 Doses n (%)
	Responders (48-72 hrs)		Non-responders (48-72 hrs)	
	n= 284	n= 294	n= 65	n=55
Clinical Success at EOT	256 (90.1)	266 (90.5)	37 (49.3)	30 (54.5)
Clinical Failure at EOT	28 (9.9)	28 (9.5)	28 (50.7)	25 (45.5)
Clinical Success at FV	254 (89.4)	262 (89.1)	41 (63.1)	35 (63.6)
Clinical Failure at FV	30 (10.6)	32 (10.9)	24 (36.9)	20 (36.4)

Source: Reviewer Table

Analyses of Prior and Concomitant Drug Therapies

Prior Drug Therapies

The prior drug therapy of interest was prior antibiotic use due to its potential to impact treatment comparisons. However, prior antibiotic use in this trial was rare. According to Reviewer analyses, there were 32/698 (4.6%) of patients who had prior antibiotic use 14 days prior to the first dose based on their CRF. This is well below the allowable limit for prior antibiotic use which is 25% of patients based on the Agency guidance. In addition, these patients fared similarly with clinical response rates on Day 3-4 of 13/19 (68.4%) in the single dose arm and 9/13 (69.2%) in the two-dose arm. Due to the small percentage of patients using prior antibiotics and the lack of a pronounced treatment difference, prior antibiotic use likely had little influence on treatment comparisons.

Reviewer Comments: *Any allowable prior (or concomitant) drug or therapy is generally a concern in non-inferiority trials because extensive use can seriously confound treatment comparisons and make treatments appear more similar than they really are. However, prior antibiotic use in this trial was not a major concern. Reviewer interest was instead on concomitant drugs or therapies that could have a strong influence on the primary/secondary outcomes. These analyses are presented in the* ***Appendix****.*

Concomitant Drug Therapies

The Reviewer considered the influence of allowed study adjunctive medications (i.e. Aztreonam and Metronidazole) up through the EOT visit and also up through the FV. Among those patients using these adjunctive medications, patients in the dalbavancin single dose arm fared substantially worse, as shown in **Table 12**. Therefore, the use of these allowable concomitant medications was unlikely to favor the dalbavancin single dose arm in treatment comparisons of success rates at EOT and FV.

Review Comments: *Patients using concomitant medications (e.g. aztreonam and metronidazole) was not a major concern in the primary analysis as these patients were also non-responders in the primary analysis of 48-72 hours.*

Table 12: Success Rates in Patients Receiving Aztreonam or Metronidazole

	Study 303		
Assessment	**Dalbavancin 1 Dose (n=33)** n (%)	**Dalbavancin 2 doses (n=45)** n (%)	**Treatment Difference (95% CI)**
EOT	24 (72.7)	42 (93.3)	-20.6 (-38.7, -4.4)

FV	26 (78.8)	39 (86.7)	-7.9 (-26.5, 9.0)

Source: Partially Adapted from Applicant Tables 14.2.16.21 & 14.2.17.21 in CSR

Additional Sensitivity Analyses

Additional sensitivity analyses were conducted to assess the robustness of the results using different efficacy criteria including success requiring a larger percent reduction in lesion area, requiring the absence of all signs or individual signs of infection, time to percent reduction in lesions size, and success rates based on investigator assessment. Additionally subgroup analyses were conducted by considering concomitant non-drug therapies as well as concomitant drug therapies. All of these analyses showed results consistent with overall results. Details of these analyses are included in the **Appendix**.

3.2.4.3 Efficacy Conclusions

The primary analysis of this trial showed that clinical responder rates at 48 to 72 hours post-baseline in the ITT population were 284/349 (81.4%) for dalbavancin single dose vs. 294/349 (84.2%) for dalbavancin two doses, a treatment difference of -2.9% (95% CI: -8.5, 2.9). These results supported the non-inferiority of dalbavancin single dose since the lower 95% confidence limit for the treatment difference was -8.5% which exceeded -10%, the minimum allowable limit based on the pre-specified 10% NI margin.

Key secondary analyses of clinical status at end of treatment (EOT) on Day 14-15 and clinical status at the final visit (FV) on Day 28 also showed similar success rates between the treatments. Success rates for clinical status at EOT and at FV for dalbavancin single dose versus dalbavancin two doses were 293/349 (84.0%) vs. 296/349 (84.8%), a difference of -0.9% (95% CI: -6.3, 4.6) and 295/349 (84.5%) vs. 297/349 (85.1%), a difference of -0.6% (95% CI: -6.0, 4.8), respectively.

In addition to the above primary and secondary analyses, the Reviewer conducted several sensitivity analyses. These analyses showed that primary and secondary analysis results were generally robust across a variety of Reviewer specifications relating to the analysis population, subgroups based on potential confounding variables (e.g. prior/concomitant antibiotic use) and methodologies and criteria used for outcome assessment (e.g. responder/success rates when requiring larger % reductions in lesion area). The Reviewer also conducted exploratory analyses such as analyses of concordance/discordance with reasons for failures or indeterminate assessments at later visits in responders at 48-72 hours. All of these analyses showed results that were consistent with overall results. Details of these analyses are included in **Section 3.2.4.2** and in the **Appendix**.

3.3 Evaluation of Safety

The Reviewer did not identify any serious safety issues specific to dalbavancin single dose. Overall, Study 303 showed similar rates of TEAEs across treatment groups at 22.3% (single

dose) vs. 21.1% (two doses), similar rates for serious TEAEs (2.0% vs. 1.4%, respectively) and similar rates of TEAEs related to study drug (7.2% vs. 7.5%, respectively). The time to onset and durations of TEAEs were also similar between treatment arms. The particular TEAEs most commonly related to study drug were nausea, headache, vomiting and dizziness were generally low and did not differ greatly between the treatment groups.

Reviewer Comments: *This statistical review is primarily focused on efficacy rather than safety. For more details regarding the safety review, refer to the safety review conducted by Dr. Rama Kapoor.*

From **Table 13**, the numbers of patients with TEAEs appeared to be similar across treatment groups when considering the various categories for TEAEs shown below.

Table 13: Overview of Adverse Events (Safety Population)

	Dalbavancin Treatment Group, n (%)	
	Single-Dose (N = 349)	**Two-Dose (N = 346)**
Number of patients who experienced at least one:		
Any adverse event	**78 (22.3)**	**73 (21.1)**
Any TEAE	**70 (20.1)**	**69 (19.9)**
TEAEs by Intensity		
Mild	43 (12.3)	38 (11.0)
Moderate	19 (5.4)	24 (6.9)
Severe	8 (2.3)	7 (2.0)
TEAE Related to Study Drug, regardless of severity	**25 (7.2)**	**26 (7.5)**
Mild	23 (6.6)	17 (4.9)
Moderate	1 (0.3)	6 (1.7)
Severe	1 (0.3)	3 (0.9)
TEAE Leading to Premature Discontinuation	**6 (1.7)**	**5 (1.4)**
Serious TEAE	**7 (2.0)**	**5 (1.4)**
Related to Study Drug	0	2 (0.6)
Leading to premature discontinuation	3 (0.9)	1 (0.3)
Death	1 (0.3)	1 (0.3)

n = Number of patients with ≥1 occurrence of an adverse event; N = Number of patients in the safety population; TEAE = Treatment-emergent adverse event.
Source: Applicant Table 29 of CSR

Table 14 shows the number of treatment-emergent adverse events. The most common TEAE in both treatment groups was nausea: 12 patients (3.4%) in the single-dose group and 7 patients (2.0%) in the two-dose group. Rates of other adverse events were low in both arms at 1.7% or lower. In comparison to the two-dose arm, the single dose arm showed slightly higher rates of nausea, headache, vomiting, diarrhea and dizziness.

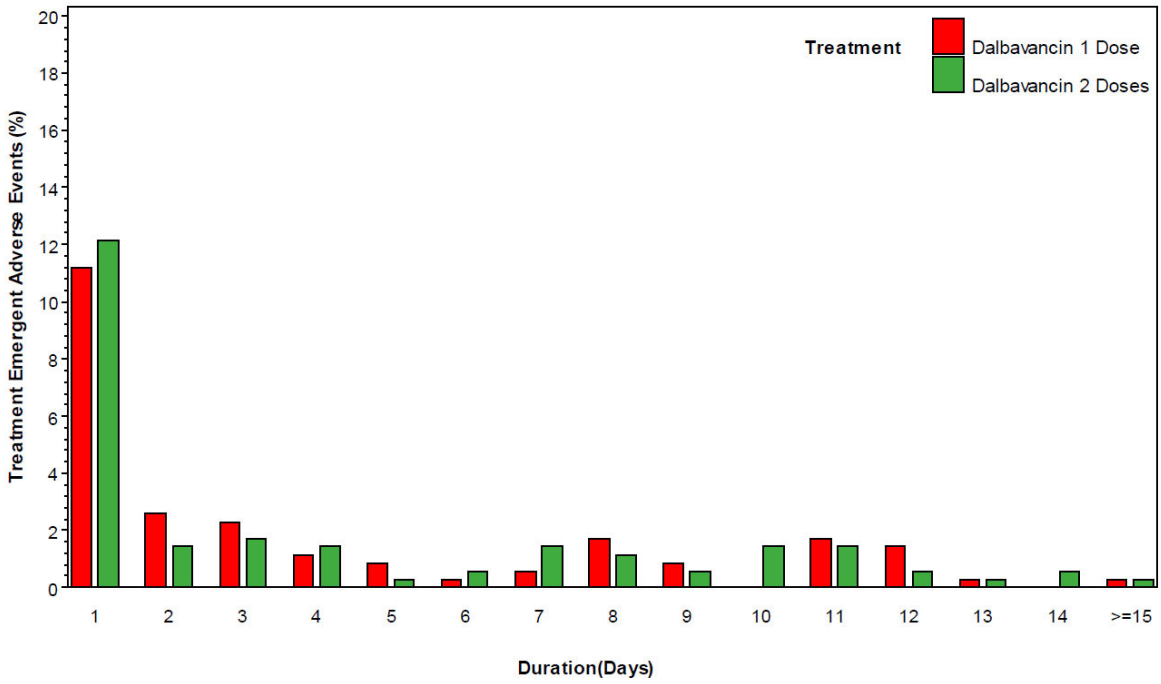
Table 14 Treatment-Emergent Adverse Events ≥1% by Decreasing Frequency

MedDRA Preferred Term	Dalbavancin Treatment Group, n (%) Single-Dose (N = 349)	Two-Dose (N = 346)
Number of events	**115**	**119**
Patients with at least 1 event	**70 (20.1)**	**69 (19.9)**
Nausea	12 (3.4)	7 (2.0)
Headache	6 (1.7)	4 (1.2)
Vomiting	6 (1.7)	3 (0.9)
Diarrhea	4 (1.1)	2 (0.6)
Dizziness	4 (1.1)	0
Cellulitis	1 (0.3)	5 (1.4)
Chills	0	4 (1.2)
Localized infection	0	5 (1.4)

Source: Applicant Table 30 of CSR

Figure 3 shows the duration of adverse events occurring in the study. Many of the adverse events observed lasted less than one day. There do not appear to clear treatment differences relating to the duration of adverse events.

Figure 3: Duration of Adverse Events



Source: Applicant Figure 11 in CSR

4. SPECIAL/SUBGROUP POPULATIONS

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

Table 15 compares 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 that consistently favored either treatment arm. In both treatment arms, clinical response rates tended to be lower in patients ≥ 65 years as well as in patients who were African-American. Note, however, that analyses in the ≥ 65 years of age and the African-American subgroups were limited by small numbers.

Table 15: Responder Rates at 48-72 hours by Age, Gender, Race and Region (ITT)

Variable / Subgroup	Trial 303 (n=698)		
	Dalbavacin 1 Dose (N=349) n (%)	Dalbavancin 2 Doses (N=349) n (%)	Difference (95% CI))
Age			
< 65	254 /308 (82.5%)	255 /300 (85.0%)	-2.5 (-8.4, 3.4)
≥ 65	30 /41 (73.2%)	39 /49 (79.6%)	-6.4 (-24.5, 11.2)

Gender			
Male	168 /204 (82.4%)	174 /203 (85.7%)	-3.4 (-10.6, 3.8)
Female	116 /145 (80.0%)	120 /146 (82.2%)	-2.2 (-11.3, 6.9)
Race			
White	260 /312 (83.3%)	267 /311 (85.9%)	-2.5 (-8.3, 3.2)
African American	16 /28 (57.1%)	21 /31 (67.7%)	-10.6 (-34.4, 14.1)
Other	8/9 (88.9%)	6/6 (100%)	-11.1 (-44.7, 31.8)
Region			
North America	129 /158 (81.6%)	134 /160 (83.8%)	-2.1 (-10.6, 6.3)
All other regions	155 /191 (81.2%)	160 /189 (84.7%)	-3.5 (-11.2, 4.1)

Source: Reviewer Table

4.2 Subgroup Analyses by Other Variables

Table 16 compares responder rates at 48-72 hours in subgroups based on other variables. Responder rates tended to be lower in the dalbavancin single dose arm among patients who at baseline were febrile or met SIRS criteria. Treatment differences were most pronounced among patients meeting SIRS criteria at baseline with rates of 108 /148 (73.0%) vs. 127 /154 (82.5%), a difference of -9.5 (95% CI: -18.9, -0.1).

Reviewer Comments: *In the subgroup of patients meeting SIRS criteria at baseline, the upper limit of the 95% CI treatment difference in responder rates at 48-72 hours is slightly below 0 (i.e. at -0.1) which would indicate a marginal finding of inferiority assuming a controlled statistical setting. However, interpretation of this finding is less clear in the current setting where statistical testing was not performed in controlled manner and involved the post-hoc testing of a large number of subgroups. This can lead to serious inflation of the overall type I error rate. The unclear interpretation of this finding underlies the need of having a second study which may or may not confirm this finding.*

When considering all patients (both treatment arms combined), lower responder rates were observed in patients who at baseline were afebrile, had cellulitis, or had met SIRS criteria.

Table 16: Responder Rates at 48-72 hours by Other Variables (ITT)

Variable / Subgroup	Trial 303 (n=698)		
	Dalbavacin 1 Dose (N=349) n (%)	Dalbavancin 2 Doses (N=349) n (%)	Difference (95% CI)
Fever Status			
Febrile	243 /290 (83.8%)	250 /283 (88.3%)	-4.5 (-10.3, 1.2)
Afebrile	41 /59 (69.5%)	44 /63 (69.8%)	-0.3 (-16.7, 15.9)
Infection Type			

Cellulitis	120 /165 (72.7%)	130 /166 (78.3%)	-5.6 (-14.9, 3.7)
Major Abscess	75 /88 (85.2%)	82 /91 (90.1%)	-4.9 (-15.1, 5.0)
Wound Infection	89 /96 (92.7%)	82 /92 (89.1%)	3.6 (-5.0, 12.6)
Bacteremia at Baseline (micro-ITT)			
Yes	10 /12 (83.3%)	10 /10 (100.0%)	-16.7 (-45.5, 14.4)
No	174 /198 (87.9%)	181 /210 (86.2%)	1.7 (-5.0, 8.3)
SIRS Criteria at Baseline			
Yes	108 /148 (73.0%)	127 /154 (82.5%)	-9.5 (-18.9, -0.1)
No	176 /201 (87.6%)	167 /195 (85.6%)	1.9 (-4.9, 8.8)
Enrolled Prior to vs. After Interim Analysis			
Prior to	99 /124 (79.8%)	104 /127 (81.9%)	-2.1 (-11.9, 7.8)
After	185 /225 (82.2%)	190 /222 (85.6%)	-3.4 (-10.3, 3.5)

Source: Reviewer Table

In addition to the subgroup analyses performed for the primary analysis variable of the clinical responder rate at 48-72 hours, subgroup analyses looking clinical status at EOT for the stratification variables used at randomization of 'infection type' and 'region' were considered. 'Prior use of antibiotics' was an additional stratification factor considered at randomization and was discussed in section 3.2.4.2. These analyses can be used to support primary analysis findings as well as to confirm the robustness of the key secondary analysis findings.

Table 17 compares clinical status at EOT by 'infection type' and 'region'. There were no notable differences observed between the treatment arms. Among all patients, those with cellulitis at baseline showed lower success rates at EOT (as well as lower responder rates at 48-72 hours, as was observed in **Table 16**).

Table 17: Clinical Status at EOT by Stratification Variables at Randomization (ITT)

Variable / Subgroup	Trial 303 (n=698)		
	Dalbavacin 1 Dose (N=349) n (%)	Dalbavancin 2 Doses (N=349) n (%)	Difference (95% CI))
Prior Use of Antibiotics			
Yes	16 /19 (84.2%)	8 /13 (61.5%)	22.7 (-8.3, 52.7)
No	277 /330 (83.9%)	288 /336 (85.7%)	-1.8 (-7.3, 3.7)
Infection Type			
Cellulitis	134 /165 (81.2%)	136 /166 (81.9%)	-0.7 (-9.2, 7.7)

Major Abscess	77 /88 (87.5%)	82 /91 (90.1%)	-2.6 (-12.5, 7.0)
Wound Infection	82 /96 (85.4%)	78 /92 (84.8%)	0.6 (-9.8, 11.2)
Region			
North America	128/158 (81.0%)	135/160 (84.4%)	-3.4 (-11.8, 5.0)
All other regions	165/191 (86.4%)	161 /189 (85.2%)	1.2 (-5.9, 8.4)

Source: Reviewer Table

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Findings

There were no major statistical issues identified with the findings in this study. However, the Reviewer considers there to be a limitation with the overall study design and the replication of evidence:

Study design limitation: The primary objective of this trial is to compare a single dose regimen of 1500mg on Day 1 to a comparator regimen of 1000mg on Day 1 and 500mg on Day 8. A key question relates to the effect of the 500mg dose on Day 8. However, this trial is limited in its ability to address this question since the assessment of the primary endpoint was on Day 3-4 which is before patients in the comparator regimen would have received their second dose (i.e. 500mg on Day 8). Key secondary analyses of success rates at EOT and FV may also be inadequate in addressing this question since there is no scientifically justified NI margin at these time points.

Reviewer Comments: *The primary assessment on Day 3-4 was selected because evidence of a 10% NI margin can be supported at Day 3-4 [3,4] but may not be clear at EOT or FV. To help address this issue, the Division also required that the trial meet a 15% threshold for the analysis of clinical success rates at FV. However, a 15% threshold was not chosen based on a scientific justification.*

Replication of evidence: In assessing the efficacy of dalbavancin single dose, reliance is on findings from a single NI study. Interpretation of some of the results can be potentially limited without the benefit of replicative evidence from another trial. For example, subgroup analyses showed responder rates among patients meeting SIRS criteria at baseline as being lower in the single dose arm at 108 /148 (73.0%) vs. 127 /154 (82.5%), a difference of -9.5 (95% CI: -18.9, -0.1). However, conclusions regarding such findings by themselves may still be unclear due to post-hoc nature of the statistical testing where the potential for inflation of the overall type I error rate cannot be ascertained.

Reviewer Comments: *There are other limitations in relying on evidence from a single study. For example, issues with study conduct, investigator biases, site integrity in this trial could have a major impact on the overall evidence of efficacy and safety.*

5.2 Collective Evidence

There is no collective evidence of efficacy since only a single pivotal Phase 3 study is submitted. Limitations in performing a single study are explained above.

5.3 Conclusions and Recommendations

In summary, there were no major statistical issues identified in this submission. Although the majority of comparisons in Trial 303 tended to be slightly less favorable in the dalbavancin single dose arm, treatment differences were still robust under the assumption of non-inferiority using a 10% NI margin. However, there are still some limitations which should be noted, as discussed in **Section 5.1**. For example, the Reviewer identified a few subgroups where primary and secondary analysis findings could potentially be less favorable to the dalbavancin single dose arm (e.g. patients meeting SIRS criteria or having fever at baseline), **Table 16**. In addition, lower success rates at EOT and FV were observed in the dalbavancin single dose arm among patients requiring the use of concomitant drug therapies (e.g. aztreonam or metranidazole), **Table 12**. However, the interpretation of such findings may be challenging without the benefit of having a second ABSSSI trial. (b) (4)

5.4 Labeling Recommendations

Negotiations regarding the product labeling are ongoing. Reviewer/Team Leader recommendations to the Division regarding the CLINICAL STUDIES section of the most recent label have included the following:

- (b) (4)
- Clarifying some of the notation (e.g. limiting use of terms such as 'ITT') and footnotes.
- Other editorial changes.

Reviewer Comments: (b) (4)

(b) (4)

6. REFERENCES

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3. Snodgrass WR, Anderson T. Sulphanilamide in the Treatment of Erysipelas. Br Med J, 1937;2:1156-9.

4. Snodgrass WR, Anderson T. Prontosil in Erysipelas. Br Med J, 1937;2:101-4.

5. Guidance for Industry on Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (dated October 2013)

7. APPENDIX

Responder When Rates Requiring Larger Percent Reductions in Lesion Area

FDA Reviewer sensitivity analyses assessed the robustness of the primary endpoint with a particular focus on the effect due to required reductions in lesion area. In order for the primary analysis findings to be robust, favorable treatment comparisons should be independent of the degree of % reduction lesion size area to be a responder as well as the timing of the assessment. Robust findings across various cut-offs in the % reduction in lesion area required to be a responder also serves to minimize the potential influence from misclassification error and biases associated with investigator measurements of lesion length and/or width used to estimate lesion area (i.e. area = length x width).

As shown in **Table 18**, patients in the dalbavancin single dose arm generally had similar percentages of patients meeting the various cut-offs for % reduction in lesion area at both the 48-72 hour and EOT assessments as the dalbavancin two dose arm. Since there was no clear trend favoring either treatment arm when considering the various cut-offs, these findings were supportive of non-inferiority.

Table 18: Responder/Success Rates Requiring Larger % Reductions in Lesion Area, Evaluated at 48-72 hours and at EOT (ITT)

Cut-off for % Decrease in Lesion Area	Study 303		
	Dalbavancin 1 Dose (n=349) n (%)	**Dalbavancin 2 Doses (n=349)** n (%)	**Treatment Difference (95% CI)**
At 48-72 hours			
≥ 30%	267 (76.5)	269 (77.1)	-0.6 (-6.9, 5.7)
≥ 40%	237 (67.9)	230 (65.9)	2.0 (-5.0, 9.0)
≥ 50%	201 (57.6)	202 (57.9)	-0.3 (-7.6, 7.0)
At EOT Assessment			
≥ 90%	277 (79.4)	280 (80.2)	-0.9 (-6.8, 5.1)
≥ 95%	257 (73.6)	266 (76.2)	-2.6 (-9.0, 3.9)
100%	237 (67.9)	241 (69.1)	-1.2 (-8.0, 5.8)

Source: Reviewer Table

Analyses of Time to Percent Reduction in Lesion Area

The Reviewer conducted exploratory analyses of time to percent reduction in lesion area. The percent reductions considered in these analyses were ≥ 20% reduction (i.e. the requirement for reduction in lesion area in order to be a responder at Day 3-4) and a ≥ 90% reduction (i.e. the requirement for reduction in lesion area in order to be a clinical success at FV). These analyses may reveal whether there is a time component associated with the reduction in lesion area. However, these analyses had several limitations:

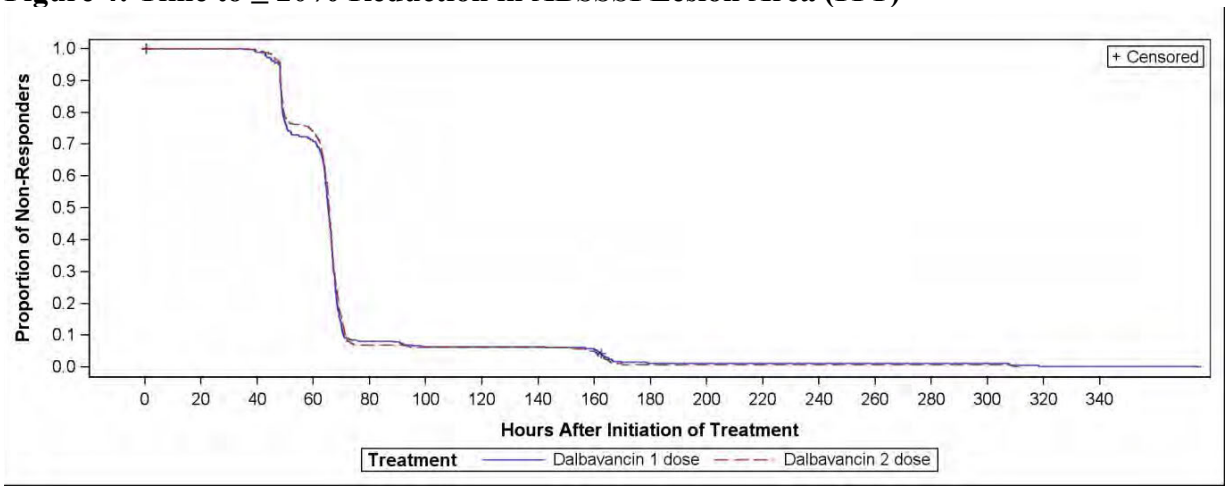
- They did not have accurate findings since the study was not designed to assess the time component and the number of time points used was limited according to the visit schedule.
- They were descriptive in nature since no non-inferiority margin can be used to compare treatment arms.
- They were not statistically controlled
- They only addressed lesion areas, ignoring other important factors (e.g. use of non-study antibiotics, surgical debridements, fever, death).

As shown in **Figure 4** and **Figure 5**, Kaplan-Meier methods were used to evaluate treatment differences for time to a ≥ 20% reduction in lesion area and time to a ≥ 90% reduction in ABSSSI lesion area, respectively. Kaplan-Meier curves for time to a ≥ 20% reduction in lesion area were similar between the treatment arms (P-value =0.88 using a log rank test). Overall, a ≥ 20% reduction in lesion area was achieved for 50% of the patients within 65.6 hours after the

first dose of study drug in the single dose arm and within 65.3 hours for the two dose arm. Kaplan-Meier curves for time to a ≥ 90% reduction in lesion area were also similar between the treatment arms (P-value =0.68 using a log rank test). Overall, a ≥ 90% reduction in lesion area was achieved for 50% of the patients within 66.8 hours after the first dose of study drug in the single dose arm and within 66.5 hours for the two dose arm.

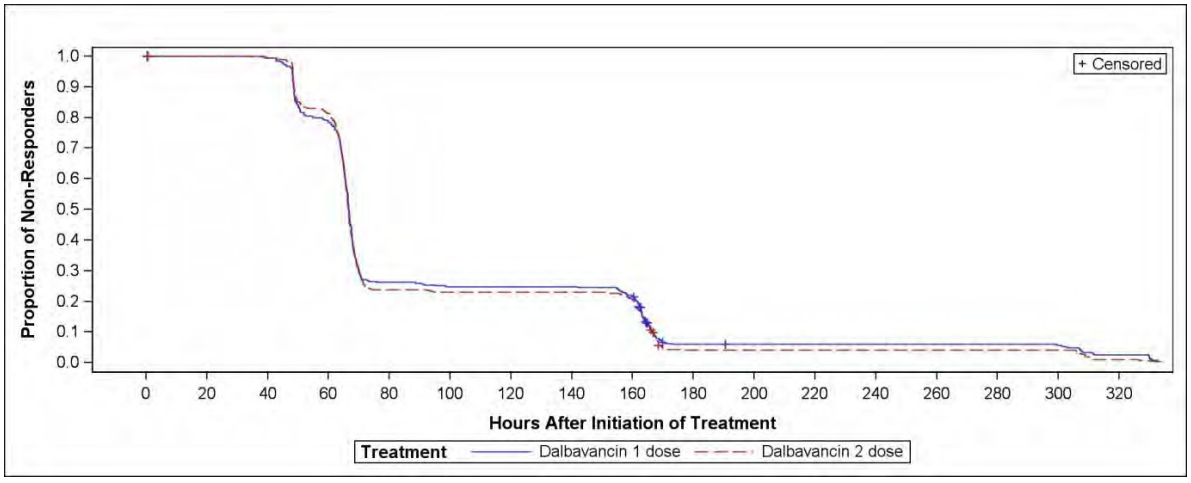
Reviewer Comments: *These estimates may have serious inaccuracies due to the limited number of time points. They should be interpreted with caution and considered only for exploratory purposes.*

Figure 4: Time to ≥ 20% Reduction in ABSSSI Lesion Area (ITT)



Source: Partially adapted from Applicant Figure 6 in CSR

Figure 5: Time to ≥ 90% Reduction in ABSSSI Lesion Area (ITT)



Source: Partially adapted from Applicant Figure 7

Reasons for Failure at EOT/FV Among Responders

Table 19 explores the reasons for failure at EOT and Final Visit (FV) among responders. This table shows that responders in each study arm are failing for similar reasons at both the EOT and FV assessments. Therefore, we can conclude that the choice of study drug is not showing a relationship to any particular reason for failure. Similar reasons for failure in responders among the treatment arms would be supportive of primary analysis findings.

Reviewer Comments: *Although reasons for failure were similar across the two treatments, they were not similar across the EOT and FV assessments among all responders. For example, responders at FV failed more often as a result of missing data or receiving non-study systemic antibacterials while responders at EOT failed more often due to lesion size not decreasing enough or due to local signs of infection not satisfying success criteria at EOT/FV.*

Table 19: Reasons for Failure at EOT/FV among Responders at Day 3-4

All Failures (Clinical Failures & Indeterminates at EOT/FV)	**Dalbavacin 1 Dose N=284**	**Dalbavancin 2 Doses N=294**	**Dalbavacin 1 Dose N=284**	**Dalbavancin 2 Doses N=294**
	At EOT		**At FV**	
All Failures	**28 (9.9%)**	**28 (9.5%)**	**30 (10.6%)**	**32 (10.9%)**
Indeterminates	**8 (2.8%)**	**11 (3.7%)**	**18 (6.3%)**	**21 (7.1%)**
No EOT/FV visit, missing all measurement data	8 (2.8%)	11 (3.7%)	17 (6.0%)	18 (6.1%)
Have EOT/FV visit, but Data are Missing	0	0	1 (0.4%)	3 (1.1%)
Clinical Failures	**20 (7.0%)**	**17 (5.8%)**	**12 (4.2%)**	**11 (3.7%)**
Lesion size at EOT/FV did not decrease from baseline ≥ 80% (EOT) or ≥ 90% (FV)	13 (4.6%)	11 (3.4%)	6 (1.6%)	5 (1.7%)
Temperature at EOT/FV >37.6C	0	1 (0.3%)	0	0
Local sign of heat/warmth and fluctuance not improved or worse than mild (EOT) or not resolved (FV)	3 (1.1%)	3 (1.0%)	1 (0.4%)	1 (0.3%)
Local sign of tenderness and swelling worse than mild	6 (2.1%)	2 (0.7%)	0	0
Purulent Drainage is same/worse from baseline or worse than mild (wound infections only)	2 (0.7%)	2 (0.7%)	1 (0.4%)	0
Received non-study systemic antibacterial for ABSSSI	3 (1.1%)	1 (0.3%)	4 (1.4%)	5 (1.7%)
Death	1 (0.4%)	0	1 (0.4%)	0

Source: Reviewer Table

Analyses of Concomitant Non-drug Therapies

The clinical team expressed concerns regarding the use of non-drug therapies such as surgical treatment in potentially influencing outcomes, especially in patients with cellulitis. Therefore, the Reviewer conducted a sensitivity analysis examining clinical response in all subjects who received surgical treatment versus those who were treated only with study drug. The Reviewer then conducted another sensitivity analysis making similar comparisons in the subgroup of patients with cellulitis. These analyses can determine whether non-drug therapies may have benefitted dalbavancin single dose in treatment comparisons. These analyses may also provide some insight into the degree to which surgery can confound therapeutic response.

The Reviewer first considered the overall effect of all non-drug adjunctive therapies initiated within 72 hours after start of study drug. These analyses are shown in **Table 20**. Comparisons of success rates in patients receiving non-drug therapies (as opposed to those not receiving non-drug therapies) did not appear to favor patients in the dalbavancin single dose arm. However, we also note that responder rates were clearly higher in patients receiving non-drug therapies. This could slightly favor treatment comparisons due to a decrease in variance associated with higher overall rates.

Reviewer Comments: *Although use of non-drug therapies did not appear to favor the treatment drug in Trial 303, it has the potential to drive the overall response rate higher and make it easier to show non-inferiority. This remains a concern in future ABSSSI trials.*

Table 20: Responder/Success Rates in Patients Receiving vs. Not Receiving Non-drug Adjunctive Therapies (ITT)

Study 303			
Endpoint	**Dalbavancin 1 Dose (n=349)** n (%)	**Dalbavancin 2 Doses (n=349)** n (%)	**Treatment Difference (95% CI)**
Responder Rates at Day 3-4			
Received Non-Drug Therapies through Day 3-4	205/238 (86.1)	213/239 (89.1)	-3.0 (-9.0, 3.0)
Received no Non-Drug Therapies through Day 3-4	79/111 (71.2)	81/110 (73.6)	-2.5 (-14.2, 9.4)
Success Rates at EOT			
Received Non-Drug Therapies through EOT	206/241 (85.5)	219/244 (89.8)	-4.3 (-10.3, 1.6)
Received no Non-Drug Therapies through EOT	87/108 (80.6)	77/105 (73.3)	7.2 (-4.2, 18.6)
Success Rates at FV			

Received Non-Drug Therapies through FV	207/242 (85.5)	217/245 (88.6)	-3.0 (-9.1, 3.0)
Received no Non-Drug Therapies through FV	88/107 (82.2)	80/104 (76.9)	5.3 (-5.6, 16.3)

Source: Reviewer Table

In **Table 21**, the Reviewer considered the influence of non-drug therapies specifically in patients with cellulitis. In this subgroup, there tended to be a more pronounced disparity in the responder/success rates based on whether non-drug therapies were received up to the assessment visit (i.e. up to Day 3-4, EOT and FV). In both the overall population and the subgroup of patients with cellulitis, patients in the dalbavancin single dose arm performed consistently worse than patients in the dalbavancin two dose arm when non-drug therapies were received.

Table 21: Responder/Success Rates in Patients with Cellulitis Receiving vs. Not Receiving Non-drug Adjunctive Therapies (ITT)

Study 303			
Endpoint	**Dalbavancin 1 Dose (n=349) n (%)**	**Dalbavancin 2 Doses (n=349) n (%)**	**Treatment Difference (95% CI)**
Responder Rates at Day 3-4			
Received Non-Drug Therapies through Day 3-4	60/76 (79.0)	72/84 (85.7)	-6.8 (-19.2, 5.1)
Received no Non-Drug Therapies through Day 3-4	60/89 (67.4)	58/82 (70.7)	-3.3 (-17.0, 10.6)
Success Rates at EOT			
Received Non-Drug Therapies through EOT	65/79 (82.3)	78/87 (89.7)	-7.4 (-18.6, 3.3)
Received no Non-Drug Therapies through EOT	69/86 (80.2)	58/79 (73.4)	6.8 (-6.1, 19.8)
Success Rates at FV			
Received Non-Drug Therapies through FV	64/80 (80.0)	78/88 (88.6)	-8.6 (-20.1, 2.4)
Received no Non-Drug Therapies through FV	71/85 (83.5)	59/78 (75.6)	7.9 (-4.6, 20.5)

Source: Reviewer Table

Success Rates Based on Investigator Assessment

Table 22 shows findings from sensitivity analyses considering the effect of the investigator assessment on key secondary results. These findings showed both treatment arms were similar with respect to success rates based on investigator assessment at EOT and FV.

Table 22: Secondary Analyses of Investigator Assessment at EOT, FV (ITT)

Study 303			
Endpoint	**Dalbavancin 1 dose (n=349)** n (%)	**Dalbavancin 2 doses (n=349)** n (%)	**Treatment Difference (95% CI)**
Investigator Assessment at EOT[1]	321 (92.0)	319 (91.4)	-0.6 (-4.8, 3.6)
Investigator Assessment at FV[1]	313 (89.7)	313 (89.7)	0.0 (-4.6, 4.6)

Source: Reviewer Table

[1] Patients with missing data at the respective visit are included in the denominator

Rates of Absence of All Local Signs

Table 23 shows that there were no major differences in rates of absence of local signs at Day 3-4, Day 8, EOT and at FV. However, slightly lower rates were observed at the final visit in the dalbavancin single dose arm at 72.5% vs. 75.9%, a difference of -3.4% (95% CI: -9.9, 3.1).

Table 23: Rates of Absence of All Local Signs of Infection by Visit

Visit[1]	**Study 303 (n=698)**		
	Dalbavancin Single dose (n=349) # (%)	**Dalbavancin Two doses (n=349)** # (%)	**Treatment Difference (95% CI)**
Day 3-4	6 (1.7)	5 (1.4)	0.3 (-1.8, 2.4)
Day 8	73 (21.0)	76 (21.8)	-0.9 (-7.0, 5.2)
EOT	188 (53.9)	190 (54.4)	-0.6 (-8.0,6.8)
FV	253 (72.5)	265 (75.9)	-3.4 (-9.9, 3.1)

Source: Reviewer Table

[1] Patients with missing data at the respective visit are included in the denominator

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Christopher Kadoorie, Ph.D.

Date: 12/15/2015

Concurring Reviewer: Karen Higgins, Sc.D., Statistical Team Leader

cc:
Chris Davi, M.S., Project Manager
Dmitri Iarikov, M.D., Ph.D., Medical Team Leader
Rama Kapoor, M.D., Medical Reviewer
Sumathi Nambiar, M.D., Division Director
Christopher Kadoorie, Ph.D., Primary Statistical Reviewer
Karen Higgins, Sc.D., Statistical Team Leader
Daphne Lin, Ph.D., Biometrics Deputy Division Director
Dionne Price, Ph.D., Biometrics Division Director
Lillian Patrician M.S., M.B.A., Mathematical Statistician

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

/s/

CHRISTOPHER E KADOORIE
12/15/2015

KAREN M HIGGINS
12/15/2015
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 021-883	Supplement-003, Submission Date(s): 07/20/2015
Drug	Dalbavancin
Trade Name	DALVANCE for Injection
OCP Reviewer	Yang He, Ph.D.
OCP Team Leader	Seong H. Jang, Ph.D
PM Team Leader	Jeffry Florian, Ph.D.
OCP Division	DCP4 and DPM
OND division	DAIP
Sponsor	Durata Therapeutics, Inc.
Relevant IND(s)	IND 60613
Submission Type; Code	Efficacy Supplement
Formulation; Strength(s)	Single-use, clear glass vials containing sterile powder equivalent to 500 mg of anhydrous dalbavancin
Indication	For the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms
Dosage and Administration	Single IV administration of 1500 mg infused over 30 min

BACKGROUND

Dalbavancin is a lipoglycopeptide antibacterial drug and is active against susceptible Gram-positive microorganisms, including *Staphylococcus aureus* (including methicillin-resistant strains [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, Group G Streptococci and viridans group streptococci. The original NDA of dalbavancin was approved for acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms with 1000 mg followed one week later by 500 mg on 05/23/2014. After the approval for the two-dose regimen, the Sponsor conducted a new Phase 3 study DUR001-303 to evaluate efficacy and safety of a single 1500 mg dalbavancin dose in comparison to the already approved two-dose regimen. In this supplement, the Sponsor is seeking a single 1500 mg dose regimen as an alternative to the approved two-dose regimen of 1000 mg on Day 1 and 500 mg on Day 8.

The results of Study DUR001-303 adequately support the efficacy and safety of a single 1500 mg dose regimen. The primary endpoint in this ABSSSI trial was the clinical response rate where responders were defined as patients who had at least a 20% decrease from baseline in lesion area 48 to 72 hours after randomization without receiving any rescue antibiotic therapy. The secondary endpoint was the clinical success rate at a follow-up visit occurring between Days 26 and 30, with clinical success defined as having at least a 90% decrease from baseline in lesion size, a temperature of 37.6° C or lower, and meeting pre-specified criteria for local signs: purulent discharge and drainage absent or mild and improved from baseline (for patients with wound infections), heat/warmth and fluctuance absent, swelling/induration and tenderness to palpation absent or mild. The results demonstrated similar clinical successful rate for these two endpoints in the Intent-to-Treat (ITT) population (At 48-72 hours: single dose 81.4 % vs. two-dose 84.2% [difference = -2.9 (95% CI, -8.5 to 2.8)]; At Day 26-30, single dose 84.5% vs. two-dose 85.1%) and the clinically evaluable (CE) population (At Day 26-30: single dose 92.3 % vs. two-dose 92.5%). Results were similar in the mITT population and in all pre-specified sensitivity analyses of the primary endpoint. The Sponsor indicated that non-inferiority of the single dose group to the two-dose group was concluded.

Overall, the proportion of patients with treatment-emergent adverse events (TEAEs) in the dalbavancin single-dose treatment group and the dalbavancin two-dose treatment group were similar (78/349 [22.3%] versus 73/346 [21.1%]). The most common (≥ 1%) of TEAEs in the single-dose and two-dose treatment groups were nausea, headache, vomiting, diarrhea, dizziness, cellulitis, chills and localized infection. Most TEAEs were mild or moderate. Changes in clinical chemistry and hematology parameters from Baseline were similar between the two treatment groups.

The current supplemental NDA submission includes an in vitro drug-drug interaction study, an animal dose fractionation study, and a population PK analysis report by combining data from the new single dose Phase 3 study with other patient trials containing PK data to refine the PK model.

Most of the clinical pharmacology related materials for dalbavancin were included in the original NDA submission, which has been reviewed in 2013 (refer to clinical pharmacology review dated 03/2014). The purposes of this review are as follows:

1. To assess the pharmacometrics analysis results based on the updated PK and PD dataset including the new single dose Phase 3 study.

2. To evaluate the newly conducted in vitro drug-drug interaction and animal dose fractionation studies.

3. To assess the appropriateness of the proposed dalbavancin susceptibility breakpoint against *Staphylococcus aureus.*

4. To provide labeling recommendations on the dalbavancin label proposed by the Sponsor.

RECOMMENDATIONS:

The Office of Clinical Pharmacology /Division of Clinical Pharmaceutical IV (OCP/DCP-IV) has reviewed NDA 21883 S-003. From a Clinical Pharmacology perspective, the recommendations below need to be conveyed to the Sponsor.

1. A single dose of 1125 mg is recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min).
2. Dalbavancin susceptibility breakpoint against the target pathogens is recommended to be 0.25.

1 ASSESSMENT OF DOSE RECOMMENDATION IN PATIENTS WITH RENAL IMPAIRMENT

In the current PopPK modeling analysis report, the Sponsor simulated dalbavancin PK profiles in severe renal impairment (CLCR<30 mL/min) following a single 1000 mg dose, by assuming half of the typical clearance value of the popPK model estimate. The results of this simulation were used to support dose recommendation for patients with severe renal impairment. Please see the Pharmacometrics (PM) review in APPENDIX 1 for more details. Based on the modeling and simulation results, the proposed single (b) (4) mg dose is predicted to provide a mean dalbavancin $AUC_{0\text{-}15days}$ of 17,085 µg/ml·hr in patients with severe renal impairment, which was 12.4% lower than the mean $AUC_{0\text{-}15days}$ of 19,519 µg/ml·hr after a single 1500 mg to-be-approved dose in patients with normal renal function. No variability of PK parameters was taken into account. Considering the estimated inter-individual variability of CL (22%) in the present popPK modeling analysis, the predicted low exposure following 1000 mg dose in patients with severe renal impairment appears acceptable in matching dalbavancin exposure to subjects with normal renal function receiving 1500 mg dose.

In the original NDA resubmission (2013), the Sponsor also included the pharmacokinetics of dalbavancin in subjects with severe renal impairment (CLCR <30 mL/min) and end-stage renal disease (ESRD) immediately before and after 3 hours of hemodialysis in Study VER001-11. **Table 1** summarizes the PK results. The Clinical Pharmacology reviewer assessed the PK data from this study and concluded that the originally proposed dose for patients with severe renal impairment based on the modeling analysis in the first 2005 NDA submission was not appropriate (see the Clinical Pharmacology review dated 09/20/2005). The Agency further demonstrated that the 750 mg dalbavancin followed by 375 mg one week later in subjects with severe renal impairment appeared to best match the plasma concentrations and exposure over 7 and 14 days of dalbavancin compared to normal subjects receiving the approved two doses.

Table 1. Mean (SD) dalbavancin plasma pharmacokinetic parameters for subjects with normal renal function and severe renal impairment or ESRD *(From the clinical pharmacology review dated 09/20/2005)*

	Severe Renal Impairment[a] (500 mg) Group A1	Severe Renal Impairment[a] (1000 mg) Group A2	End Stage Renal Disease (pre-dialysis) (500 mg) Group B1	End Stage Renal Disease (post-dialysis) (500 mg) Group B2	Normal Renal Function[b] (500 mg) Group C
	(N = 6)	(N = 4)	(N = 3)	(N = 3)	(N = 6)
C_{max} (mg/L)	136.5 (21.6)	315.3 (89.7)	140.7 (26.4)	145.8 (71.5)	137.3 (39.5)
% CV	15.83	28.46	18.76	49.05	28.78
T_{max} (hr)[c]	0.54	0.55	0.55	0.58	0.51
Range	(0.50 – 0.65)	(0.50 – 0.60)	(0.50 – 0.62)	(0.50 – 0.65)	(0.50 – 0.52)
$AUC_{0\text{-day7}}$ (hr*mg/L)	6077 (1392)	10653 (1474)	6069 (1768)	4969 (1153)	5245 (1661)
% CV	22.91	13.84	29.13	23.20	31.68
$AUC_{0\text{-day14}}$ (hr*mg/L)	10412 (2658)	18698 (1780)	10620 (2881)	8500 (2297)	7971 (2422)
% CV	25.53	9.52	27.13	27.02	30.39
$AUC_{0\text{-inf}}$ (hr*mg/L)	24074 (6613)	44497 (11483)	19772 (5065)	15587 (6050)	12219 (3298)
% CV	27.47	25.81	25.62	38.81	26.99
V_{SS} (L)	13.2 (2.9)	14.2 (0.8)	12.8 (3.4)	14.6 (3.2)	15.0 (4.2)
% CV	21.70	5.62	26.39	22.00	28.22
CL (L/hr)	0.0222 (0.0064)	0.0238 (0.0068)	0.0264 (0.0063)	0.0350 (0.0113)	0.0429 (0.0092)
% CV	28.88	28.73	23.98	32.24	21.37
$t_{½}$ (hr)	454 (102)	469 (103)	376 (63)	347 (78)	333 (91)
% CV	22.52	21.96	16.83	22.37	27.36

This recommended two-dose regimen of dalbavancin (750 mg on Day 1 and 375 mg a week later) was subsequently approved in patients with severe renal impairment in 2013, and the total dosage strength is 1125 mg. To be consistent with the total dosage strength of the approved two-dose regimen, the Reviewer recommends that a single 1125 mg dose of dalbavancin be more appropriate for patients with severe renal impairment, compared to the Sponsor proposed single (b) (4) dose, given the dose-proportional and linear PK properties of IV dalbavancin. In addition, the Reviewer recommended 1125 mg dose in patients with severe renal impairment would produce almost identical mean AUC over 7 and 15 days as the one following the single 1500 mg dose in subjects with normal renal functions, and the Cmax by the recommended dose will be within the range of PK variation, based on the updated popPK modeling results.

2 ASSESSMENT OF IN VITRO DDI STUDY AND ANIMAL PK/PD STUDY

2.1 Evaluation of Human Cytochrome P450 Induction Potential of Dalbavancin in Human Hepatocytes

The study results showed that dalbavancin at concentrations of up to 1000 μg/mL had no induction potential for CYP1A2. Due to the effect of Tween-80 and Captisol®, which were added to reduce dalbavancin nonspecific binding and increase dalbavancin solubility, on the induction of CYP 2B6 and 3A4, the induction potential of dalbavancin on these two enzymes may not be evaluated properly in the current study. Thus, it is not conclusive whether dalbavancin can potentially induce CYP 2B6 and 3A4 in human hepatocytes.

2.2. In Vivo Pharmacodynamic Activity of Dalbavancin

The proposed bioanalytical method (LC-MS/MS) was successfully qualified for the analysis of dalbavancin in mouse plasma samples. At the comparable dose levels, dalbavancin concentrations in plasma determined in the present animal PK/PD study were lower than those determined in the previous animal PK/PD study. In the present animal PK/PD study, dalbavancin concentrations were assayed with the new LC-MS/MS, whereas dalbavancin concentrations were assayed with a bioassay method in the previous animal PK/PD study. The concentrations determined by the new LC-MS/MS are considered more reliable because the LC-MS/MS method measured specifically the dalbavancin molecule while the bioassay used in the previous study might have measured overall antimicrobial activity, which was then transformed into corresponding dalbavancin concentration. Dalbavancin PK/PD targets for bacterial stasis and killing were derived against a group of glycopeptide-resistant *S. aureus* isolates at dose levels that correspond to clinically achievable exposures. The mean 24 h total dose and PK/PD targets free drug AUC/MIC for net bacterial stasis, 1-log kill and 2-log kill for all isolates are listed in the table below.

Endpoint	24 h dose (mg/kg)	24 h free drug AUC/MIC
Net Stasis	14.4	27.1
1-log kill	29.9	53.3
2-log kill	61.1	111.1

The proposed animal PK/PD target value for bacterial stasis based on the results of the present animal PK/PD study (i.e., 27.1 of 24 h free AUC/MIC for stasis) appears reasonable.

3 ASSESSMENT OF SUSCEPTIBILITY BREAKPOINT

The exposure-response (ER) analysis in the present Pharmacometrics (PM) report indicated that there was lack of relationship between the PK/PD index (AUC/MIC) and clinical efficacy. Thus, in contrast to the previous PM analysis result (see Clinical Pharmacology review dated 03/04/2014 for details), no attempt of using clinical ER relationship was made in support of susceptibility breakpoint in the present analysis. Instead, using a new animal AUC/MIC target value obtained from a recent animal dose fractionation study, the Sponsor performed a target attainment analysis and indicated that the nonclinical PK/PD cutoff would be able to support a breakpoint up to (b) (4) mg/L. Based on this nonclinical PK/PD cutoff information, the Sponsor proposed to increase the current susceptibility breakpoint from 0.12 to (b) (4) mg/L against *Staphylococcus aureus*. No scientific rationale was provided in support of the proposed breakpoint of (b) (4) mg/L.

With review of the present target attainment analysis, the methodology and result of target attainment analysis appear reasonable from a technical point of view. However, the nonclinical PK/PD cutoff from this analysis is much higher than the microbiology surveillance MIC90 of 0.06 mg/L and most resistant pathogens in the clinical studies. In the all 3 Phase 3 studies, the most resistant *S. aureus* was MIC of 0.25 mg/mL isolated from a total of 2 patients, and the clinical efficacy at 72 hours was 50% in these patients, although both patients were cured at end of treatment. Based on the available information from microbiology, nonclinical study, and clinical study (**Table 2**), the proposed nonclinical PK/PD cutoff of (b) (4) mg/mL alone may be excessive and is not considered to provide supportive information for determination of susceptibility breakpoint, since this PK/PD cutoff was derived from a hypothetical simulation and the value is not able to reflect current clinical situation. The Reviewer recommends that the ultimate determination of the dalbavancin breakpoint should rely on microbiology surveillance MIC90 and clinical data. In addition, as communicated with the Microbiology Reviewer, variability of MIC measurement is usually within 2-fold dilutions. Therefore, we recommend increasing the susceptibility breakpoint to 0.25 mg/L against *Staphylococcus aureus* for the proposed single 1500 mg dose as well as the previously approved 1000 mg followed one week later by 500 mg dalbavancin dose.

Table 2. Supportive Information in All Three Disciplines for Susceptibility Breakpoint from the Sponsor and the FDA

	Sponsor		***FDA***	
	2013	***2015***	***2013***	***2015***
Microbiology Surveillance, MIC90 (mg/L)	0.06	0.06	0.06	0.06
Nonclinical PK/PD cutoff (mg/L)	(b) (4)		0.12-0.25	Not considered*
Clinical ER Data (mg/L)	(b) (4)	n/a	0.06	n/a
Most Resistant *S. aureus* in clinical studies (mg/L)	0.25 (n=2)	0.25 (n=2)	0.25 (n=2)	0.25 (n=2)
Recommended Dalbavancin Breakpoint (mg/L)	(b) (4)		**0.12**	**0.25**

* Although the Sponsor proposed nonclinical PK/PD cutoff appears reasonable based on the new animal study, it is not used to support the ultimate breakpoint determination in the clinical pharmacology assessment.

Appendix 1. Pharmacometric Review for Study Report DAL-MS-01

1 SUMMARY OF REVIEW FINDINGS

The current population PK (popPK) modeling analysis report (DAL-MS-01) updated the popPK model of dalbavancin (POP-PK-PROJ-2013) by including patient PK data from the newly completed Phase 3 study DUR001-303. The final PK dataset consisted of 2310 concentrations measurements from 703 subjects across 4 studies (VER001-4, VER001-5, VER001-9, DUR001-303). As reported in the original NDA, the best structural model was a three-compartment model with a zero order input and first order elimination with random effects on the main clearance and the compartmental volume parameters. The estimated population total clearance (CL) was 0.0531 L/hr and the population steady state volume of distribution (V_{ss}) was 15.1 L. The current popPK model addressed several issues identified with the previously reported modeling analysis, re-evaluated total clearance as a single parameter (instead of using separated renal and non-renal components in the previous popPK analysis), and re-evaluated covariate effects. The final model included relationships for: creatinine clearance (CLCR), weight, and albumin on CL; weight and albumin on central volume of distribution (V1); weight, albumin, and age on one peripheral volume of distribution (V2); and weight and albumin on the other peripheral volume of distribution (V3). The impact of the covariates was modest and in line with the previous observations of intrinsic factors on the popPK of dalbavancin.

Pharmacokinetic/pharmacodynamic (PK/PD) analyses for dalbavancin were conducted using individual AUC/MIC (area under concentration-time curve to minimum inhibitory concentrations ratio) of subjects with PK measurements from Study DUR001-303, against four clinical endpoints: clinical response at 48-72 hours; clinical status at end of treatment; clinical status at final visit; and investigator assessed status at final visit. Based on univariate logistic regression modeling result, no statistically significant exposure-response (E-R) relationships were identified.

Target attainment analysis was undertaken to re-evaluate nonclinical PK/PD cutoff, which could be subsequently used to inform susceptibility breakpoint in conjunction with microbiology surveillance study results and clinical efficacy outcomes.

Based on a new 2015 neutropenic mouse model study (DAL-MC-01), the Sponsor considered that a non-clinical free AUC/MIC stasis target of 27.1 was predictive of clinical efficacy in patients with ABSSSI. The results of the probability of target attainment (PTA) analysis using Monte Carlo simulation indicated that, the approved and newly proposed dosing regimens would provide more than 90% of simulated subjects with AUC/MIC >27.1(i.e., the non-clinically derived target) at MIC ≤ (b) (4) Please see the review of the Study Dal-mc-01 (**Appendix 2**) for the rationale of the proposed PK/PD target. Thus, the Sponsor proposed that simulations with the new target were supportive of an MIC breakpoint of (b) (4) for both the 1000 and 1500 mg doses.

Based on our review of the submitted pharmacometric report, the updated popPK modeling analysis is considered to address the issues (*outlined in 3.1.3.2*) in the previous popPK model and improved PK model stability and performance. There was flat E-R relationship observed in Study DUR001-303. The Reviewer agrees that flat ER

relationship was likely due to the narrow exposure range resulting from a single dose of dalbavancin administered to the patients in the Phase 3 study and a narrow range of resistant pathogens (high MICs) found in the patient population. From a technical perspective, the current target attainment analysis appears reasonable. However, as noted in our clinical pharmacology review for the original NDA submission, the determination of breakpoints involves multiple disciplines providing clinical and microbial interpretations as well as the probability of nonclinical target attainment analysis. The proposed nonclinical PK/PD cutoff of (b) (4) mg/mL based on the current target attainment analysis is not aligned with the microbiology surveillance MIC90 of 0.06 mg/mL. In addition, this proposed breakpoint exceeds the clinical experience by multiple steps, and from available clinical data it cannot be definitively concluded that response would remain unchanged for higher MIC values. This PK/PD cutoff alone would not provide supportive information for determination of susceptibility breakpoint, since this PK/PD cutoff was derived from a hypothetical simulation and the value is not able to reflect the current clinical situation. The Reviewer recommends that the ultimate determination of the dalbavancin breakpoint should rely on the microbiology surveillance MIC90 and reflect MIC values with which there is clinical efficacy experience rather than the derived PK/PD cutoff.

2 BACKGROUND

Dalbavancin is a lipoglycopeptide antibacterial drug. The original NDA of dalbavancin was approved for acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms with 1000 mg followed one week later by 500 mg on 05/23/2014. Dosage adjustment is needed for patients with severe renal impairment (creatinine clearance < 30 mL/min), and the recommended dose is 750 mg IV on Day 1 and (b) (4) mg IV on Day 8 in such patients. Previous pharmacokinetic (PK) analyses, based on data from Studies VER001-4, VER001-5, and VER001-9 (pop-pk-proj-2013, Projections Research), found that the PK of dalbavancin is described by a three compartment linear model.

After the approval, the Sponsor conducted another Phase 3 study (Study DUR001-303) comparing the safety and efficacy of a single IV dose of 1500 mg dalbavancin dosed on day 1 to the approved regimen of 1000 mg IV on day 1 followed by 500 mg IV on day 8. PK assessments were included in the Phase 3 study. The current study report (DAL-MS-01, dated 06/19/2015) updates the popPK model by including the DUR001-303 PK sampled patients in the analysis. Results from the popPK analysis were used to assess the relationship between dalbavancin exposure for the primary endpoint (clinical response at 48-72 hours) and three secondary endpoints. Simulations with the revised popPK model were used to assess PK/PD target attainment for various MIC levels.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK analysis (DAL-MS-01)

3.1.1 Objectives:

- Update the previously developed popPK model based on data from Study DUR001-303
- Data permitting, establish an exposure-response model that is predictive of clinical outcome based on data from Study DUR001-303
- Conduct target attainment simulations to determine a PK/PD breakpoint based on data from Study DUR001-303.

3.1.2 Studies included in the PopPK analysis

The PK data used in the current population analysis included all available concentration data collected from Studies VER001-4, VER001-5, VER001-9, and DUR001-303 (b) (4)

Appendix 2. Review of In Vivo Pharmacodynamic Activity of the Glycopeptide Dalbavancin

Study Number: DAL-MC-01

Study Title: In Vivo Pharmacodynamic Activity of the Glycopeptide Dalbavancin
Investigator(s): (b) (4)

Bioanalytical Assay Site: (b) (4)

Objective
The current studies were designed to define the AUC/MIC PK/PD target for dalbavancin against *S. aureus* strains with dalbavancin MICs at or above the current FDA breakpoint (>0.12 μg/mL) and some of which were vancomycin intermediate (VISA).

Materials and Methods:
Bacteria, media, and antibiotic.
Seven strains of *Staphylococcus aureus* (including 4 vancomycin intermediate *S. aureus* [VISA]) were used for these experiments. Organisms were grown, subcultured, and quantified in Mueller-Hinton broth (Difco Laboratories, Detroit, MI) and Mueller-Hinton agar (Difco Laboratories). Dalbavancin was supplied by Durata Therapeutics (Batch Number WP4003).

In vitro susceptibility studies.
The MIC values of the isolates used in the neutropenic mouse model were determined by (b) (4) The MIC values of dalbavancin and comparator agents were determined using CLSI reference broth microdilution methodology (M07-A10; CLSI 2015). All isolates were tested in triplicate and all quality control (QC) results were within the published QC ranges (M100-S25; CLSI 2015).

Murine thigh infection model.
Six-week-old, specific pathogen-free, female ICR/Swiss mice weighing 23 to 27 g were used for all studies. A neutropenic model was used for all studies. The mice were rendered neutropenic (neutrophils, $<100/mm^3$) by injecting them with cyclophosphamide intraperitoneally 4 days (150 mg/kg of body weight) and 1 day (100 mg/kg) before the thigh infection study and 100 mg/kg every 48 h after the start of infection until the end of the study. Broth cultures of freshly plated bacteria were grown to logarithmic phase overnight to an absorbance at 580 nm of 0.3. After dilution 1:10 in fresh Mueller-Hinton broth, the bacterial counts of the inoculum was 107.08±0.10 CFU/ml. Thigh infections with each of the isolates were produced by injection of 0.1 ml of inoculum into the thighs of halothane-anesthetized mice 2 h before therapy with dalbavancin. At the end of the study period, the thighs were processed for CFU determination.

Plasma pharmacokinetics.
Single-dose plasma PK studies were performed with thigh-infected mice given intraperitoneal doses (0.2 ml/dose) of dalbavancin (2.5, 10, 40, 80 and 160 mg/kg). Blood was removed from groups of three mice per dose at ten time points (0.5, 1, 2, 3, 4, 6, 12, 24, 48, and 72 h) after dosing. The plasma was separated by centrifugation, and dalbavancin plasma concentrations

were measured by an LC/MS/MS assay. Pharmacokinetic constants, including the elimination half-life, AUC, and Cmax, were calculated by using a noncompartmental model. The AUC was estimated at 24, 36, 48, 72, and 96 h and was extrapolated to infinity. An accumulation factor was considered for the shorter-dosing-interval studies (q12h and q24h). A protein binding value of 98.4% was utilized based upon prior studies in this model.

Bioanalytical Methodology

Swiss ICR mouse plasma (K_2EDTA) samples from Durata Study DAL-MC-01 were analyzed for dalbavancin. A total of 150 mouse plasma samples were received on 28 April 2015. The mouse plasma samples were analyzed for Dalbavancin by a qualified high-performance liquid chromatographic-triple quadrupole mass spectrometric (LC-MS/MS).

Briefly, the bioanalytical method entailed (b) (4)

Assay qualification was completed on 11 May 2015 prior to sample analysis. Duplicate standard curves were prepared by spiking blank mouse plasma with Dalbavancin at nine concentrations in the range of 0.0500 µg/mL (LLOQ) to 50.0 µg/mL (ULOQ). Quality Control (QC) samples (n=6), at two concentrations (0.150 and 40 µg/mL), were analyzed within the run to establish precision and accuracy during qualification. Qualification QC Precision (%CV) was < 3.6% and Accuracy (%Bias) was -10.0%. Sample analysis for this study was conducted between 12 May 2015 and 15 May 2015. The plasma samples were analyzed in two analytical runs for Dalbavancin. On sample analysis days, two standard curves were run with unknowns and QC samples (at three concentrations, namely 0.150, 20 and 40 µg/mL) and the regression equation obtained was used to calculate the concentrations of QC and unknown samples. Sample Analysis QC Precision (%CV) ranged from 5% to 6.-4% and Accuracy (%Bias) ranged from -3.5% to -10.0%.

Dilution linearity was demonstrated up to 10-fold dilution of samples, freeze-thaw stability was demonstrated for four cycles(-80 °C to RT), bench-top mouse plasma stability was demonstrated for 17.25 hours at room temperature and the long-term freezer storage stability (at -80 °C) was demonstrated for 28 days, and adequately cover the conditions under which study samples were analyzed.

(b) (4)(Version 1.4.2 (b) (4) was used for peak integration and data acquisition. The peak areas were imported into (b) (4)(Version 7.4.2, (b) (4) (b) (4) for linear regression analysis. The peak area ratios of Dalbavancin to IS and the concentrations of the calibration standards were fitted using a $1/x^2$ weighted regression analysis.

Treatment protocols

Two hours after infection with the seven S. aureus isolates, neutropenic mice (two mice per time point) were treated with one of seven twofold-escalating intraperitoneal doses of dalbavancin every 12 h (2.5, 5, 10, 20, 40, 80, and 160 mg/kg) over a six day treatment period. Untreated control groups were sampled at the start of therapy and at 72h. The thighs were removed from each animal and immediately processed for CFU determination. Data are expressed as the mean ± standard deviation log CFU/thigh.

Data analysis

The results of these studies were analyzed by using the sigmoid dose-effect model. To allow a comparison of the potency of dalbavancin against a variety of organisms, the Sponsor estimated the 24 h static dose and the doses required to achieve a 1 $\log_{10}$ reduction and a 2 $\log_{10}$ reduction in colony counts. The magnitude of the PK/PD index associated with each endpoint dose was calculated from the following equation: $\log_{10} D = \log_{10} [E/(Emax - E)]/(N+\log_{10} ED50)$, where E is the control growth for the static dose (D), E is the control growth - 1 log unit for a D of 1-log killing, and E is the control - 2 log units for a D of 2-log killing. The significance of differences among the various dosing endpoints was determined by using analysis of variance. The correlation between efficacy and the AUC/MIC was determined by nonlinear least-squares multivariate regression [redacted] (b) (4) The coefficient of determination (R^2) was used to estimate the variance that could be due to regression with each of the PK/PD indices.

Results:

Bioanalytical analysis

Calibration standards were prepared fresh daily on wet ice by spiking 25.0 µL of the appropriate spiking solution into blank mouse plasma. The calibration curve is presented in **Table 1**.

Table 1. Calibration Curve Summary for Dalbavancin in Mouse Plasma

Run Date	Run Number	Slope	Intercept	R-Squared	LLOQ µg/mL	ULOQ µg/mL
12-May-2015	1	0.604488	0.006115	0.9972	0.0500	50.0
15-May-2015	2	0.581604	0.005609	0.9923	0.0500	50.0
Mean		0.593046	0.005862	0.9948		
n		2	2	2		

Response = Slope * Concentration + Intercept.

Analytical quality controls (QC) at three levels were assayed in at least duplicate in each analytical run. In addition, dilution QCs were analyzed in at least triplicate in each analytical run (**Table 2**).

Table 2. Analytical QC Summary for Dalbavancin in Mouse Plasma

Run Date	Run Number	QC 1 0.150 µg/mL	QC 3 20.0 µg/mL	QC 4 40.0 µg/mL	QC 5 DIL 200 µg/mL (DF=10)[a]
12-May-2015	1	0.142	19.4	35.9	
		0.145	19.8	35.1	
		0.150	19.8	34.8	
		0.140	19.6	36.3	
15-May-2015	2	0.128	17.4	33.7	209
		0.153	20.0	40.3	213
					212
Mean		0.143	19.3	36.0	211
SD		0.00881	0.969	2.29	2.08
%CV		6.2	5.0	6.4	1.0
%Theoretical		95.3	96.5	90.0	105.5
%Bias		-4.7	-3.5	-10.0	5.5
n		6	6	6	3

a: Diluted 10-fold with blank mouse plasma.

Study organisms and dalbavancin MICs

The study organisms and the MICs for dalbavancin are listed in **Table 4**.

Table 4. Study Strains and Dalbavancin In vitro Susceptibility

Prior Study		Current Study		
Isolate	**MIC (mg/L)**	**Isolate**	**MIC (mg/L)**	**Comment**
25923	0.12	LSI653	0.25	(VAN=2)
33591	0.12	LSI1848	0.12	
31005	0.06	LSI1854	0.5	
MRSA	0.06	LSI1856	0.25	VISA (VAN=4)
Smith	0.06	LSI1857	0.25	VISA (VAN=4)
307106	0.06	LSI1861	0.25	VISA (VAN=4)
		LSI1862	0.5	VISA (VAN=4)

Plasma pharmacokinetics. The plasma pharmacokinetics of dalbavancin following intraperitoneal administration to Swiss ICR mice are shown in **Figure 1**. Peak concentrations were observed at 2-6 h. Dalbavancin exhibited relatively linear pharmacokinetics. The half-life was prolonged and varied from 4.1to 9.31 h. The present concentrations are lower than those previously reported in this model as shown in **Table 5**. The Sponsor stated that the only experimental difference between the two studies was the plasma assay method (specific LC-MS/MS in present and bioassay in the prior study).

Figure 1. Plasma pharmacokinetics of dalbavancin in mice following intraperitoneal administration. Each symbol represents the mean and standard deviation from three mice.

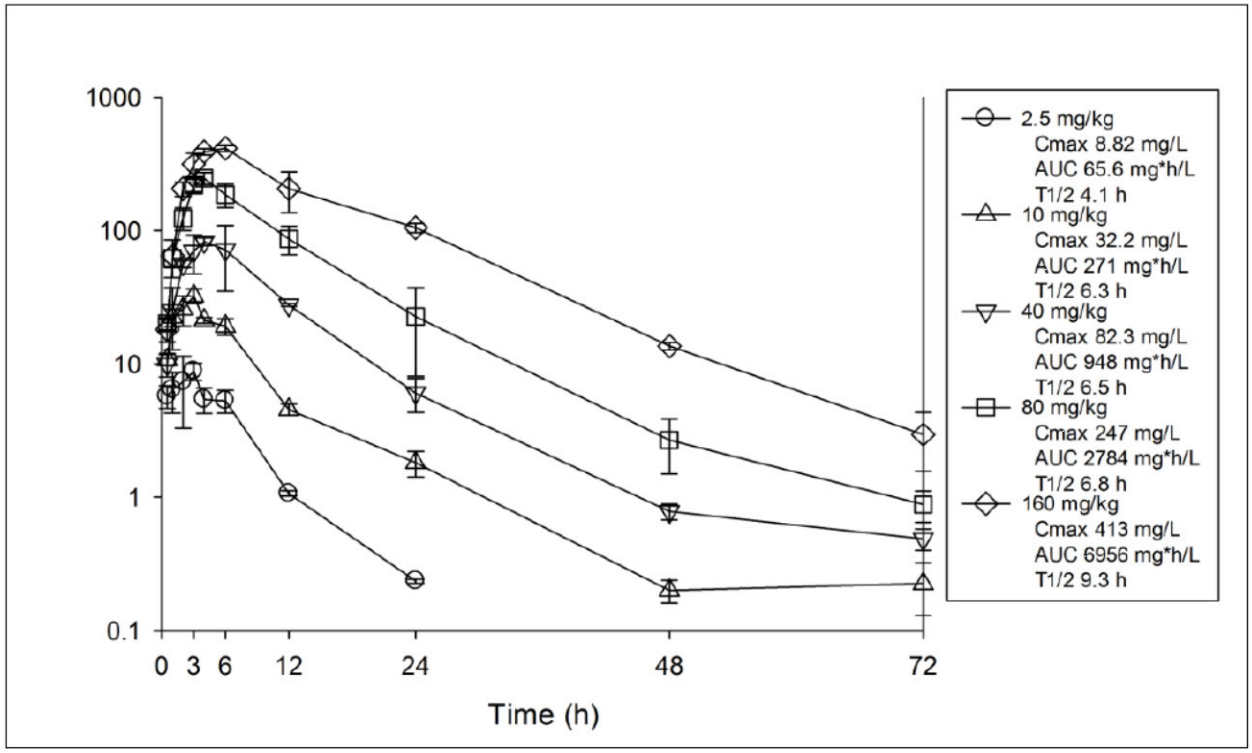
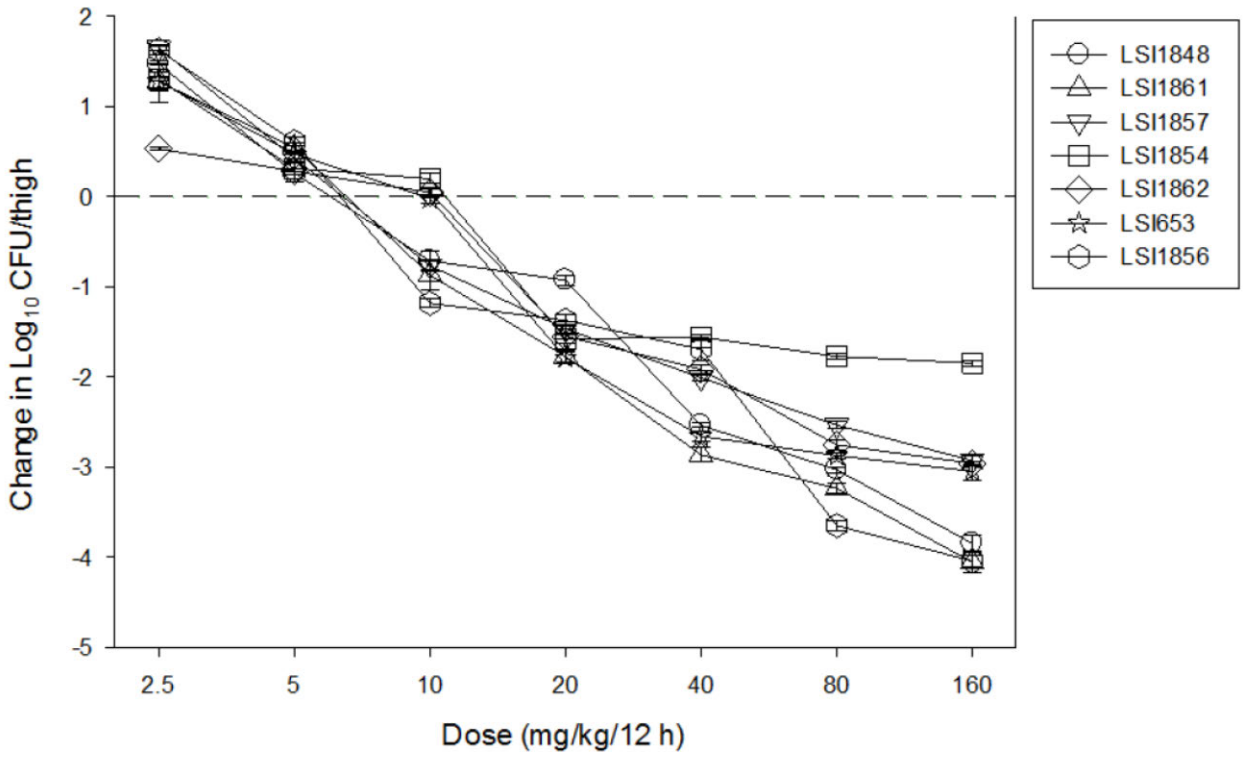


Table 5. Dalbavancin plasma pharmacokinetic parameters in mice from the present and prior study.

Dose (mg/kg)	Prior Study			Current Study		
	Cmax (µg/ml)	AUC (mg*h/L)	$T_{1/2}$ (h)	Cmax (µg/ml)	AUC (mg*h/L)	$T_{1/2}$ (h)
2.5	7.4	98	13.1	8.82	65.6	4.1
10	34.8	579	12.5	32.2	271	6.3
40	385	5360	10.4	82.3	948	6.5
80	663	10600	9.7	247	2784	6.8
160				413	6956	9.3

PK/PD index magnitude or target. At the start of therapy mice had 107.18±0.10 CFU/thigh of the infection organisms. Each of the organisms grew more than 2 $\log_{10}$ units in untreated mice over 72h (102.29±0.15). The dose response curves for the seven *S. aureus* strains are fairly similar (**Figure 2**). More than a 2 $\log_{10}$ reduction in organism burden was observed against 6 of 7 isolates. Prior PD data in this model against a set of wild-type *S. aureus* is also presented in **Table 6**. The dose levels associated with the three treatment endpoints on a mg/kg basis are somewhat lower in the present dataset than in studies with wild-type *S. aureus* isolates.

Figure 2. In vivo dose effect of dalbavancin against seven select *S. aureus* isolates using a neutropenic mouse thigh model. Each symbol represents the mean and standard deviation from four thighs



The numeric AUC/MIC values associated with each of the three treatment endpoints are also shown in **Table 6**. Net stasis was observed with a dalbavancin fAUC/MIC value near 25. fAUC/MIC values near 50 and 100 were associated with 1- and 2-log reductions in organism burdens in the neutropenic mice, respectively. These PK/PD targets are several-fold lower than those observed with wild-type *S. aureus* strains in this same model. This is in part due to lower PK concentrations measured in the present study, perhaps due to differences in assay method.

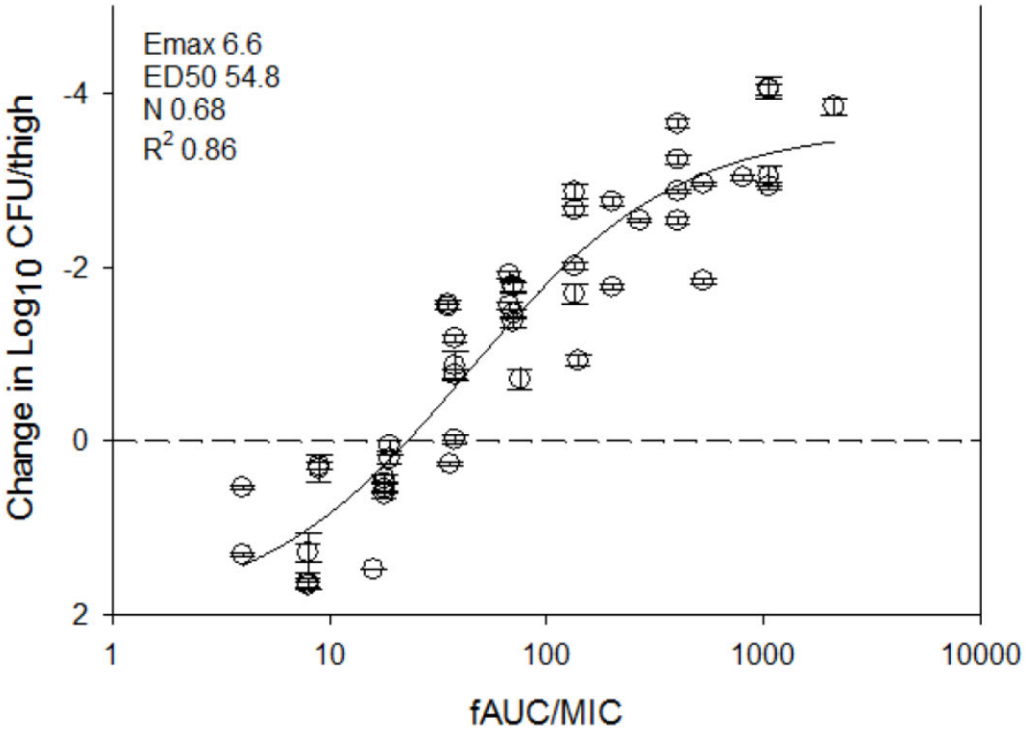
Table 6. In vivo efficacy of dalbavancin against select *S. aureus* isolates using AUC/MIC as the predictive pharmacodynamic index

	Static Dose		1 Log Kill		2 Log Kill	
Strain	24h Dose (mg/kg)	24h fAUC/MIC	24h Dose (mg/kg)	24h fAUC/MIC	24h Dose (mg/kg)	24h fAUC/MIC
LSI1848	15.17	56.49	31.45	112.81	62.75	214.21
LSI1861	13.55	25.00	24.63	45.35	44.38	77.35
LSI1857	14.34	26.59	26.72	48.74	60.05	102.72
LSI1854	15.00	13.95	35.80	31.73		
LSI1862	12.64	11.60	32.92	29.39	85.46	76.66
LSI653	14.93	27.77	27.20	49.52	54.09	93.07
LSI1856	15.21	28.32	30.88	55.49	60.05	102.73
Mean	**14.41**	**27.10**	**29.94**	**53.29**	**61.13**	**111.12**
Median	**14.93**	**26.59**	**30.88**	**48.74**	**60.05**	**97.90**
SD	**0.98**	**14.62**	**3.93**	**27.93**	**13.62**	**51.81**
Prior Data						
	Static Dose		**1 Log Kill**		**2 Log Kill**	
Strain	**24h Dose (mg/kg)**	**24h fAUC/MIC**	**24h Dose (mg/kg)**	**24h fAUC/MIC**	**24h Dose (mg/kg)**	**24h fAUC/MIC**
25923	42.7	216	51.2	250	60	289
33591	22.3	96.2	27.7	121	33.5	157
31005	49.3	483				
MRSA	37.7	374	45.3	452	53.5	519
Smith	33.5	156	50.7	248	73.5	361
Mean	**37.1**	**265**	**43.7**	**268**	**55**	**332**
Median	**37.7**	**216**	**48**	**249**	**56.8**	**325**
SD	**9.1**	**143**	**9.5**	**119**	**14**	**131**

The dalbavancin in vivo exposure response data was also considered relative to the PK/PDindex, AUC/MIC, using free drug concentrations. Using a sigmoid Emax model the data fit was strong for the seven strain dataset (R^2=0.86) as shown in **Figure 3**.

Figure 3 In vivo dose effect of dalbavancin against seven *S. aureus* isolates using a neutropenic mouse thigh model. Each symbol represents the mean and standard deviation from four thighs. The dalbavancin exposure is expressed as the free drug 24-h AUC/MIC. The burden of organisms was measured at the start and end of therapy. The horizontal line at 0 represents the burden of organisms in the thighs of mice at the start of therapy. Data points below the line represent killing and points above the line represent growth. The R^2 represents the coefficient of determination. The ED_{50} represents the AUC/MIC associated with 50% of the maximal effect

(Emax), and N is the slope of the relationship or the Hill coefficient. The line drawn through the data points is the best fit line based upon the sigmoid Emax formula.



The investigator discussed the differences in PK and PK/PD index value results obtained between the current study and the prior study. There are several possible explanations for this difference, including those related to the drug, drug assay, study design, and microbes. The investigator indicated that the drug itself was identical (except study lot) to that from the previous study (based upon discussion with the Sponsor). From the laboratory standpoint we did not observe any marked differences in appearance or solubility. As mentioned above the present study used an every 12h as opposed to 24h regimen. Based upon the prior fractionation data this should have minimal, if any, impact on the outcome. Drug resistance has been clearly linked to 'fitness cost' in some circumstances. However, in this case the specific organisms grew similarly well to those in the prior study. Finally, we have noted the difference in drug analytical method. It is possible this may contribute to the differences in the pharmacokinetic profiles. Certainly, the lower measured drug concentrations had a major impact on the lower AUC/MIC values linked to the various treatment endpoints.

Applicant's Conclusion:
The proposed bioanalytical method was successfully qualified for the analysis of dalbavancin in mouse plasma samples. All study samples received were successfully analyzed using the qualified method and the concentration data generated were reported. Based on the quality control and calibration curve data, the data submitted for dalbavancin are accurate for all of the DAL-MC-01 study samples.

Dalbavancin PD stasis and killing targets were achieved against this group of glycopeptide-resistant SA isolates at dose levels that correspond to clinically achievable exposures. The mean

24 h total dose and PD target free drug AUC/MIC for net stasis, 1-log kill and 2-log kill for all isolates are listed in the table below.

Endpoint	24 h dose (mg/kg)	24 h free drug AUC/MIC
Net Stasis	14.4	27.1
1-log kill	29.9	53.3
2-log kill	61.1	111.1

Translation of these data suggests the current human dosing regimen could achieve a 1-log kill for SA strains with dalbavancin MICs of ≤1 mg/L. Modification of clinical breakpoints should be considered based on this PD study and additional clinical data.

Reviewer's Assessment

The bioanalytical methodology (LC-MS/MS) used in this newly conducted animal study is validated and acceptable. At the comparable dose levels, dalbavancin concentrations in plasma determined in the present animal PK/PD study were lower than those determined in the previous animal PK/PD study. In the present animal PK/PD study, dalbavancin concentrations were assayed with the new LC-MS/MS, whereas dalbavancin concentrations were assayed with a bioassay method in the previous animal PK/PD study. The concentrations determined by the new LC-MS/MS are considered more reliable because the LC-MS/MS method measured specifically the dalbavancin molecule while the bioassay used in the previous study might have measured overall antimicrobial activity, which was then transformed into corresponding dalbavancin concentration. The proposed animal PK/PD target value based on the results of the present animal PK/PD study (i.e., 27.1 of 24 h free AUC/MIC for stasis) appears reasonable in comparison of 265 of the corresponding value proposed in the previous animal PK/PD study. However, in the study design, it would be more helpful if the previously used bioassay for dalbavancin measurement can be employed in the study in order to compare the assay result from the same plasma sample to the current LC-MS/MS analytical method.

Appendix 3. Review of Dalbavancin in vitro P450 induction study

Study Number: 14713
Study Completed: June 3, 2015

Study Title: Dalbavancin: Evaluation of Human Cytochrome P450 Induction Potential in Human Hepatocytes

Objective
The objective of this study was to evaluate the potential of dalbavancin to induce human cytochrome P450 (CYP) isozymes using cryopreserved plateable human hepatocytes (HH) with attention to the three major inducible drug metabolizing enzymes, i.e., CYP 1A2, 2B6, and 3A4. The induction of the CYP enzymes was assessed by measuring the expression levels of CYP mRNA. The hepatocyte viability was also evaluated at the end of incubation.

Materials and Methods:
The test article, dalbavancin, was provided by Durata Therapeutics. The positive control inducers, omeprazole (CYP1A2 Inducer), phenobarbital (CYP2B6 Inducer), rifampin (CYP3A4 Inducer), and the negative control inducer flumazenil were obtained from (b) (4) (b) (4) Cryopreserved plateable HH from three different donors (two male donors, (b) (6) and one female donor, (b) (6) were obtained from (b) (4) (b) (4)

CYP Induction Incubation in Human Hepatocytes
CYP induction potential of dalbavancin was evaluated by incubating the test article at 10, 100, and 1000 µg/mL with plated HH from three individual donors. One day after the hepatocytes were plated, HH were treated with dalbavancin, known inducers, or a known non-inducer for 3 days. Omeprazole (50 µM), Phenobarbital (750 µM), and rifampin (25 µM) were used as positive controls for the induction of CYP 1A2, 2B6, and 3A4, respectively. Flumazenil (25 µM) was used as the negative control (non-inducer).

CYP Induction Potential Assessment
At the end of incubation, the RNA of HH was isolated and the mRNA expression levels of CYP 1A2, 2B6, and 3A4 were evaluated by using real-time Polymerase Chain Reaction (qPCR) after being reverse transcribed (RT) to cDNA. The CYP induction was calculated using a standard $\Delta\Delta C_T$ method and the expression of 18S of HH was used as the reference gene.

(b) (4) (v.6.2.2, (b) (4) (b) (4) was used to acquire luminescent signals of the viability samples analyzed by plate reader.

Results:
Under experimental conditions, the presence of Tween-80 and Captisol®, which were added to prevent non-specific binding of dalbavancin and to solubilize dalbavancin, respectively, did not have significant effects on the CYP1A2 mRNA expression levels (0.81-1.28 fold) from all three donors and CYP2B6 mRNA expression levels (0.98-fold) from donor (b) (6) However, Tween-80 and Captisol® had 2.38-4.92-fold CYP2B6 mRNA induction in hepatocytes from two donors

(b) (6) In addition, CYP3A4 mRNA expression levels in hepatocytes from all donors increased from 4.16 to 13.28-fold in the presence of Tween-80 and Captisol®. Therefore, the induction potential of dalbavancin on CYP 2B6 and 3A4 mRNA may not be properly evaluated in the current study.

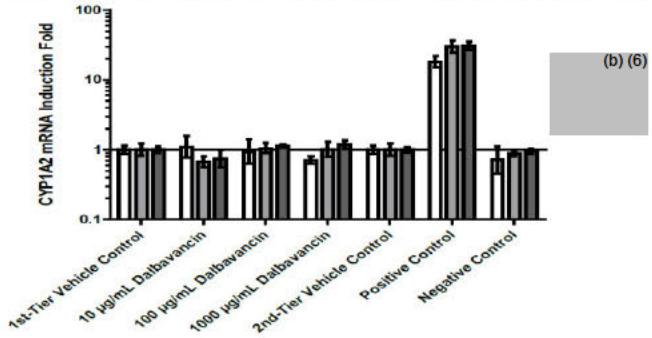
The experimental CYP induction results are summarized in **Table 1**. Under experimental conditions, dalbavancin at concentrations of up to 1000 µg/mL showed no induction potential for CYP1A2 mRNA expression levels in hepatocytes from three donors (**Figure 1**). **Figures 2** and **3** depict induction results for CYP2B6 and CYP3A4, respectively. Respective positive controls under the same conditions showed significant induction relative to untreated hepatocytes and CYP 1A2, 2B6, and 3A4 expression levels were not affected by the treatment of the negative control, flumazenil.

Table 1. Induction of CYP 1A2, 2B6 and 3A4 mRNA by Dalbavancin, Negative Control and Positive Control in Human Hepatocytes

CYP	Donor	CYP mRNA Induction Folds[a] of Hepatocytes from Three Donors with Various Treatments					
		Dalbavancin (µg/mL)			1st Tier VC[b]	NC[c]	PC[d]
		10	100	1000			
1A2	(b) (6)	1.10	0.94	0.71	0.81	0.71	18.19
		0.67	1.06	1.02	1.28	0.88	29.98
		0.74	1.13	1.19	0.93	0.95	30.58
2B6		1.40	1.08	1.45	0.98	1.12	6.45
		0.63	1.02	1.10	4.92	1.08	14.46
		1.09	1.48	2.60	2.38	1.14	15.17
3A4		1.21	1.40	2.41	13.28	0.76	214.88
		0.66	1.35	1.84	12.91	1.09	8.18
		0.96	1.63	2.98	4.16	1.07	25.44

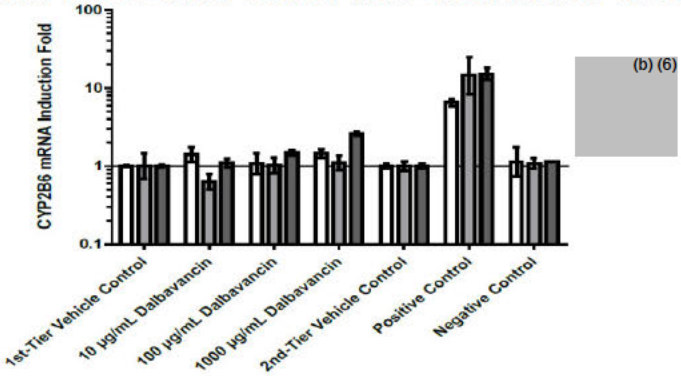
[a] Induction fold values were calculated as described in Section 5.4.4.
[b] 1st Tier VC: 1st Tier vehicle control – 0.002% Tween-80, 0.4% Captisol® and 0.1% DMSO
[c] NC: Negative control – flumazenil (25 µM) was used as the negative control treatment
[d] PC: Positive control – omeprazole (50 µM), phenobarbital (750 µM) and rifampin (25 µM) were used as the positive control treatment for CYP 1A2, 2B6 and 3A4, respectively.
Data are means of triplicate

Figure 1. Relative Induction Fold of CYP1A2 mRNA Expression Levels in Human Hepatocytes from Three Donors Treated with Dalbavancin at Three Concentrations



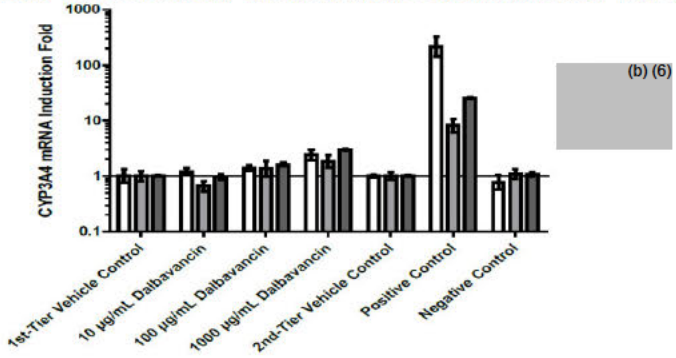
1st-Tier Vehicle control, Tween-80 0.002%, Captisol® 0.4% and DMSO 0.1%
2nd-Tier Vehicle control, DMSO 0.1%
Positive control, Omeprazole 50 µM
Negative control, Flumazenil 25 µM
Data are 2 to the power of means of triplicate. The error bars are 2 to the power of standard deviations of triplicate.

Figure 2. Relative Induction Fold of CYP2B6 mRNA Expression Levels in Human Hepatocytes from Three Donors Treated with Dalbavancin at Three Concentrations



1st-Tier Vehicle control, Tween-80 0.002%, Captisol® 0.4% and DMSO 0.1%
2nd-Tier Vehicle control, DMSO 0.1%
Positive control, Phenobarbital 750 µM
Negative control, Flumazenil 25 µM
Data are 2 to the power of means of triplicate. The error bars are 2 to the power of standard deviations of triplicate.

Figure 3. Relative Induction Fold of CYP3A4 mRNA Expression Levels in Human Hepatocytes from Three Donors Treated with Dalbavancin at Three Concentrations



1st-Tier Vehicle control, Tween-80 0.002%, Captisol® 0.4% and DMSO 0.1%
2nd-Tier Vehicle control, DMSO 0.1%
Positive control, Rifampin 25 µM
Negative control, Flumazenil 25 µM
Data are 2 to the power of means of triplicate. The error bars are 2 to the power of standard deviations of triplicate.

Under experimental conditions, dalbavancin at concentrations of up to 1000 µg/mL had no significant effect on the hepatocyte viability (**Table 2**).

Table 2. Viability of Human Hepatocytes after Induction Incubations with Various Treatments

Test Compound	Concentration	Relative Percent Viability[a] of Hepatocytes from Three Donors with Various Treatments (b) (6)		
Dalbavancin	10 µg/mL	92.2 ± 4.8	88.4 ± 7.4	101.1 ± 2.7
	100 µg/mL	95.1 ± 5.7	106.1 ± 9.2	100.8 ± 4.2
	1000 µg/mL	110.3 ± 4.9	117.6 ± 9.7	89.9 ± 2.1
1st-Tier-Vehicle Control[b]		100.0 ± 5.9	100.0 ± 11.1	100.0 ± 3.1
Omeprazole	50 µM	146.2 ± 11.5	124.0 ± 5.1	118.8 ± 2.6
Phenobarbital	750 µM	103.9 ± 8.7	96.3 ± 6.1	107.9 ± 2.2
Rifampin	25 µM	120.0 ± 3.1	109.9 ± 6.7	119.7 ± 4.5
Flumazenil	25 µM	94.4 ± 4.4	98.8 ± 5.6	97.3 ± 3.5
2nd Tier Vehicle Control[c]		100.0 ± 3.3	100.0 ± 5.4	100.0 ± 1.9

[b] 1st-Tier vehicle control contained 0.002% Tween-80 and 0.4% Captisol® and 0.1% DMSO in the incubation medium
[c] 2nd-Tier vehicle control contained 0.1% DMSO in the incubation medium

Applicant's Conclusion:
Under experimental conditions, dalbavancin at concentrations of up to 1000 µg/mL showed no induction potential for CYP1A2. Due to the effect of Tween-80 and Captisol on the induction of CYP 2B6 and 3A4, the induction potential of dalbavancin on these two enzymes may not be evaluated properly in the current study. Dalbavancin at concentrations of up to 1000 µg/mL showed no significant effects on hepatocyte viability.

Reviewer's Assessment
We agree with the Sponsor's conclusion. Based on the Clinical Pharmacology Reviewer assessment, dalbavancin showed no induction effect on CYP1A2. The potential induction effects of dalbavancin on CYP3A4 and CYP2B6 were not adequately assessed and cannot be ruled out.

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

/s/

YANG HE
12/07/2015

JEFFRY FLORIAN
12/07/2015

SEONG H JANG
12/07/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

PRODUCT QUALITY REVIEW(S)

Memorandum

Date: January 16, 2016

To: NDA 21883/S003 [Dalvance® (dalbavancin for injection), 500 mg]

From: Dorota Matecka, CMC Lead, DNDP I, Branch III

Dorota M. Matecka -S

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Date: 2016.01.20 09:04:26 -05'00'

Through: Balajee Shanmugam, Ph.D., Acting Branch Chief, DNDP I, Branch III

Re: Dalvance® Labeling

Balajee Shanmugam -S

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This memorandum is an addendum to the CMC review of the efficacy supplement NDA 21883/S003 dated December 7, 2015 (entered into Panorama on December 8, 2015). This prior-approval efficacy supplement, currently under review in DAIP, provides for an addition of a single dose regimen (1500 mg) as an alternative treatment to the originally approved two-dose regimen of 1000 mg on Day 1 and 500 mg on Day 8 in the labeling of Dalvance®. The CMC information provided in this supplement was reviewed via the CMC review dated December 7, 2015. In addition, several CMC-related minor revisions were proposed to the Dalvance® labels and the package insert via the labeling supplement, NDA 21883/S002, which included a change associated with the current efficacy supplement, i.e., a revision from the originally approved "single-dose vial" to a "single-use vial" statement on the container and carton labels. This proposed revision was intended by the Applicant to mitigate the risk of potential medication error and avoid future confusion between "single-dose vial" and "single-dose regimen". The CMC review of the labeling Supplement 002 (entered into Panorama on December 17, 2015) stated that this issue would continue to be discussed prior to approval of the current efficacy supplement.

Subsequently, this issue ("single-dose" versus "single-use") was discussed within the Office of Pharmaceutical Quality (OPQ), specifically with the members of the Office of Policy for Pharmaceutical Quality (OPPQ), Richard Lostritto and Yana Mille, who determined that this product falls into a category of single-dose containers as described in the recently published draft Guidance for Industry, "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use"(October 2015), and, therefore, recommended that the "single-dose vial" term be used in all parts of the Dalvance® labeling. However, DAIP expressed concerns that the "single-dose vial" term on a vial and carton labels of Dalvance® may be confusing and cause potential errors in dosing patients since the new single-dose regimen is now included in the labeling; therefore, DAIP believes that the term "single-use vial" is more appropriate for this product at this time.

CMC REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DNDP I, Branch III and DAIP	21883
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE
Durata Therapeutics, Inc. Harborside Financial Center, Plaza V, Suite 1900 Jersey City, NJ 07311		S-003 Efficacy July 20, 2015
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
DALVANCE®	dalbavancin	N/A

8. COMMUNICATION PROVIDES FOR:

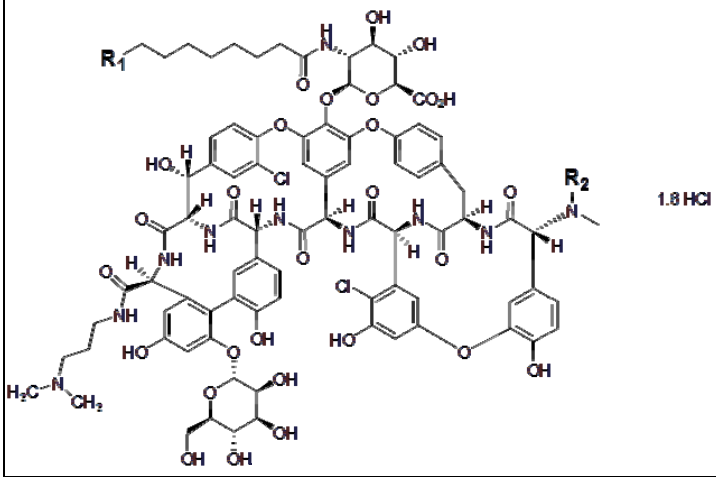
Addition of a single 1500 mg dose regimen for the treatment of acute bacterial skin and skin structure infections (ABSSSI).

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Antibacterial	Rx	N/A
12. DOSAGE FORM	**13. POTENCY**	
Powder for injection	500 mg/vial	

14. CHEMICAL NAME AND STRUCTURE

Dalbavancin (B_0): CAS Chemical Name (B0): Ristomycin A aglycone, 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-[2-deoxy-2-[(10-methyl-1-oxoundecyl)amino]-β-D-glucopyranuronosyl]-38-[[[3-(dimethylamino)propyl]amino]carbonyl]-42-*O*-α-D-mannopyranosyl-N15-methyl-;

$C_{88}H_{100}Cl_2N_{10}O_{28}$,(Dalbavancin B_0); MW = 1816.7 (free base)



15. COMMENTS

This prior-approval efficacy supplement provides for an addition of a single 1500 mg dose regimen as an alternative to the originally approved two-dose regimen of 1000 mg on Day 1 and 500 mg on Day 8 in the labeling of Dalvance®. The CMC information remains mostly unchanged from that of the approved NDA. The only CMC change associated with this efficacy supplement includes lowering a limit for endotoxins (from NMT 0.35 EU/mg to NMT 0.23 EU/mg) in the drug product specification. The CMC information provided in the supplement in support of this revision was reviewed by the Product Quality Microbiology Reviewer who concluded that the proposed change is acceptable (refer to the review by Daniel Schu entered into Panorama on October 2, 2015).

In addition, the Applicant is claiming categorical exclusion from preparation of an environmental assessment (EA). The applicant stated that the Estimated Introduction Concentration (EIC) for dalbavancin into the aquatic environment is well below the FDA guidance limit of 1 part per billion (ppb). Moreover, metabolism of dalbavancin and its degradation products would not have any impact on the EIC. The Applicant also stated that to Durata's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment and, therefore, this NDA supplement qualifies for a categorical exclusion from the requirement to prepare an EA under 21 CFR Part 25.31(b). The Applicant's request for categorical exclusion from environmental assessment is acceptable.
16. CONCLUSION AND RECOMMENDATION: This efficacy supplement is recommended for "**Approval"** from the CMC perspective.
APPROVAL

17. NAME	**18. REVIEWERS SIGNATURE**	**19. DATE COMPLETED**
Dorota Matecka	*Digital (below)*	December 7, 2015

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

Dorota M. Matecka -S

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Date: 2015.12.08 14:30:41 -05'00'

Balajee Shanmugam -S

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Product Quality Microbiology Review

01 Oct 2015

NDA: 021-883/S-003

Drug Product Name
Proprietary: Dalvance
Non-proprietary: Dalbavancin hydrochloride

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
20 July 2015	20 July 2015	N/A	21 Sept 2015

Applicant/Sponsor
Name: Durata Therapeutics International B.V.
Address: Spaces Zuidas II
Barbara Strozzilaan 101, 1083HN
Amsterdam, Amsterdam 1083 HN
The Netherlands
Representative: Ronald Trust, Ph.D., MBA, Executive Director
Telephone: (203) 871-4610

Name of Reviewer: Daniel J. Schu, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Supplement

2. SUBMISSION PROVIDES FOR: This submission provides for a revision to the dose regimen.

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Lyophilized powder for injection
- Intravenous infusion
- 500 mg/vial

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

6. PHARMACOLOGICAL CATEGORY: Antibiotic.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS: This supplement was submitted in the eCTD format.

filename: 021883s3.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 021883/S-003 is **recommended** for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

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

III. Product Quality Microbiology Risk Assessment- The proposed change to the drug product specification poses no additional risk to the microbiological quality of the subject drug product.

IV. Administrative

A. Reviewer's Signature _____
Daniel J. Schu, Ph.D.

B. Endorsement Block _____
John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer

C. CC Block
N/A

Product Quality Microbiology Assessment

Durata Therapeutics International B.V. seeks approval for a revision to the approved dose regimen of the subject drug product. The proposed change is from the approved two-dose regimen of 1000 mg on Day1 and 500 mg on Day 8 to a single 1500 mg dose regimen. There are no changes proposed to the drug product, composition, container closure system or manufacturing processes. Due to the proposed change in the dose regimen, the applicant has lowered the limit at release for bacterial endotoxins test from NMT 0.35 EU/mg to NMT 0.23 EU/mg for the subject drug product (Section 3.2.P.5.1). The bacterial endotoxins limit for parenteral drugs, defined on the basis of dose, is equal to K/M, where K is the threshold pyrogenic dose of endotoxin per kg of body weight (5.0 EU/Kg) and M is the maximum recommended human dose of product per kg of body weight in a single hour period. Assuming an average adult body weight of 70 kg, the limit was calculated by this reviewer as follows:

K/M= (5 USP-EU/kg x 70 kg) / 1500 mg= 0.23 EU/mg

Acceptable

Reviewer's Comment

Based on the proposed dose regimen, the decreased endotoxin limit complies with USP<85>. Therefore, the applicant has met regulatory expectations with regard to the proposed acceptance criteria of the bacterial endotoxins test that will be performed on the drug product prior to its release. Additionally, the applicant confirms that all commercial lots of the subject drug product meet the proposed endotoxins limit of 0.23 EU/mg (Section 3.2.P.5.6.13). The proposed change in dosing regimen poses no additional risk from the product quality microbiology perspective.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

There are no microbiology deficiencies identified.


APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

CLINICAL MICROBIOLOGY REVIEW(S)

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
(ADDENDUM)

NDA: 21-883/S003 (SDNs 220, 225, 226, 259)
Date Company Submitted: 07-20-2015, 08-12-2015, 08-13-2015, 10-15-2015
Date received by CDER: 07-20-2015, 08-12-2015, 08-13-2015, 10-15-2015
Date Assigned: 07-22-2015; 08-13-2015, 10-15-2015
Reviewer: Kalavati Suvarna, Ph.D.

NAME AND ADDRESS OF APPLICANT:

Durata Therapeutics Inc.
200 South Wacker Drive
Chicago, IL 60606

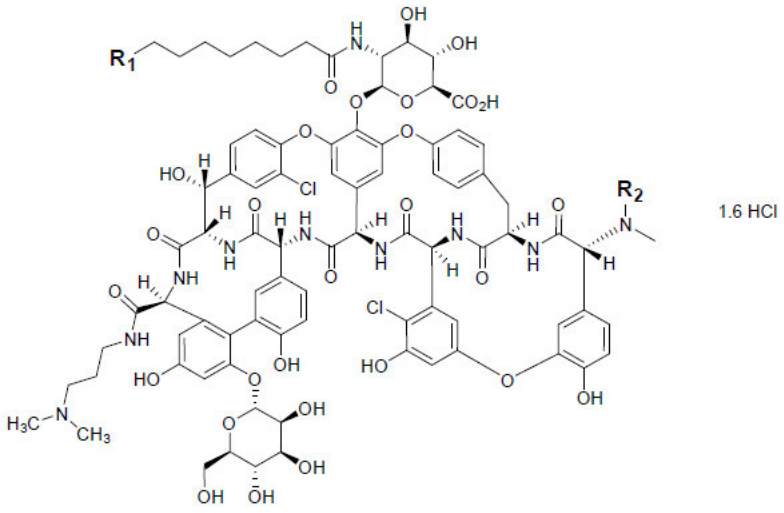
DRUG PRODUCT NAMES:

Proprietary Name: DALVANCE™

Established Name: Dalbavancin

Chemical Name: The B0 chemical name is: 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O[2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl]-38-[[3-(dimethylamino)propyl] carbamoyl]-42-O-α-D-mannopyranosyl-15-N-methyl(ristomycin A aglycone) hydrochloride.

Structural Formula: Dalbavancin is a mixture of five active homologs (A0, A1, B0, B1, and B2) with B0 being the major component of dalbavancin. The homologues share the same core structure and differ in the fatty acid side chain of the N-acylaminoglucuronic acid moiety (R1) structure and/or the presence of an additional methyl group (R2) on the terminal amino group



Dalbavancin	R_1	R_2	Molecular Formula	Molecular Weight*
A_0	$CH(CH_3)_2$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7
A_1	$CH_2CH_2CH_3$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7
B_0	$CH_2CH(CH_3)_2$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7
B_1	$CH_2CH_2CH_2CH_3$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7
B_2	$CH_2CH(CH_3)_2$	CH_3	$C_{89}H_{102}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1830.7

*Anhydrous free base

PROPOSED DOSAGE FORM AND STRENGTH:

Sterile, lyophilized preservative-free, powder containing 500 mg of dalbavancin. Each 500 mg vial of dalbavancin for injection is reconstituted and further diluted in 5% Dextrose Injection prior to administration.

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

The proposed dosing regimen is a single 1500 mg IV dose.

PROPOSED INDICATION:

Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*.

PHARMACOLOGICAL CATEGORY: Antimicrobial

DISPENSED: Rx

TYPE OF SUBMISSION: NDA Efficacy supplement

CROSS-REFERENCE: IND 060613

PURPOSE OF SUBMISSION: Prior approval efficacy supplement.

SUMMARY AND RECOMMENDATIONS:

DALVANCE™ (dalbavancin) for Injection was approved on 23 May 2014 for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of the following Gram-positive bacteria *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae,* and *Streptococcus anginosus* group (NDA 21-883). The approved adult dalbavancin dose is 1000 mg IV on Day 1 and 500 mg IV on Day 8 with dose adjustment for renally impaired patients (CRCL < 30 mg/min and not on dialysis). In this supplemental New Drug Application (sNDA) submission, the applicant has proposed an alternative dosing regimen of single dose 1500 mg IV dalbavancin for the treatment of ABSSSI caused by susceptible strains of Gram-positive bacteria.

This is an addendum to the clinical microbiology review dated 11-03-2015 for NDA21-883/S003 and supports the susceptible breakpoint of ≤0.25 mcg/mL for the bacteria included in the Indication and Usage section of the label. Although majority of the isolates (90%) of *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group, and vancomycin sensitive *Enterococcus faecalis* had a dalbavancin MIC value ≤0.12 mcg/mL, the distribution was unimodal and within the breakpoint of 0.25 mcg/mL supported by the PK-PD target attainment analyses.

SIGNATURES:

Kalavati Suvarna, Ph.D. {See appended signature}
Clinical Microbiology Reviewer Signature/Date

Avery Goodwin, Ph.D. {See appended signature}
Acting Clinical Microbiology Team Leader Signature/Date

CC:
Original NDA
DAIP CSO/Davi, Christopher

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

/s/

KALAVATI C SUVARNA
01/19/2016

AVERY C GOODWIN
01/19/2016

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA: 21-883/S003 (SDNs 220, 225, 226, 259)
Date Company Submitted: 07-20-2015, 08-12-2015, 08-13-2015, 10-15-2015
Date received by CDER: 07-20-2015, 08-12-2015, 08-13-2015, 10-15-2015
Date Assigned: 07-22-2015; 08-13-2015, 10-15-2015
Reviewer: Kalavati Suvarna, Ph.D.

NAME AND ADDRESS OF APPLICANT:

Durata Therapeutics Inc.
200 South Wacker Drive
Chicago, IL 60606

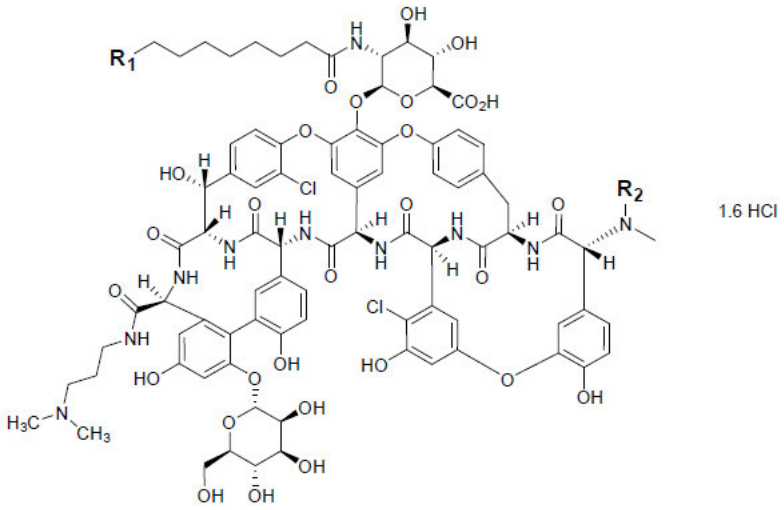
DRUG PRODUCT NAMES:

Proprietary Name: DALVANCE™

Established Name: Dalbavancin

Chemical Name: The B0 chemical name is: 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O[2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl]-38-[[3-(dimethylamino)propyl] carbamoyl]-42-O-α-D-mannopyranosyl-15-N-methyl(ristomycin A aglycone) hydrochloride.

Structural Formula: Dalbavancin is a mixture of five active homologs (A0, A1, B0, B1, and B2) with B0 being the major component of dalbavancin. The homologues share the same core structure and differ in the fatty acid side chain of the N-acylaminoglucuronic acid moiety (R1) structure and/or the presence of an additional methyl group (R2) on the terminal amino group



Dalbavancin	R_1	R_2	Molecular Formula	Molecular Weight*
A_0	$CH(CH_3)_2$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7
A_1	$CH_2CH_2CH_3$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7
B_0	$CH_2CH(CH_3)_2$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7
B_1	$CH_2CH_2CH_2CH_3$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7
B_2	$CH_2CH(CH_3)_2$	CH_3	$C_{89}H_{102}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1830.7

*Anhydrous free base

PROPOSED DOSAGE FORM AND STRENGTH:

Sterile, lyophilized preservative-free, powder containing 500 mg of dalbavancin. Each 500 mg vial of dalbavancin for injection is reconstituted and further diluted in 5% Dextrose Injection prior to administration.

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

The proposed dosing regimen is a single 1500 mg IV dose.

PROPOSED INDICATION:

Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*.

PHARMACOLOGICAL CATEGORY: Antimicrobial

DISPENSED: Rx

TYPE OF SUBMISSION: NDA Efficacy supplement

CROSS-REFERENCE: IND 060613

PURPOSE OF SUBMISSION: Prior approval efficacy supplement.

SUMMARY AND RECOMMENDATIONS:

DALVANCE™ (dalbavancin) for Injection was approved on 23 May 2014 for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of the following Gram-positive bacteria *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus* group (NDA 21-883). The approved adult dalbavancin dose is 1000 mg IV on Day 1 and 500 mg IV on Day 8 with dose adjustment for renally impaired patients (CRCL < 30 mg/min and not on dialysis). In this supplemental New Drug Application (sNDA) submission, the applicant has proposed an alternative dosing regimen of single dose 1500 mg IV dalbavancin for the treatment of ABSSSI caused by susceptible strains of Gram-positive bacteria.

The dalbavancin ABSSSI indication was approved based on two Phase 3 clinical studies (DUR001-301 and DUR001-302) that demonstrated noninferiority for the two-dose dalbavancin regimen versus twice daily vancomycin IV regimen (with option to switch to oral linezolid after 3 days). The primary efficacy evaluated early clinical response for an intent-to-treat (ITT) population at 48 to 72 hours after initiation of therapy. Clinical responders were defined as having cessation of spread of erythema, induration, and/or edema, and the absence of fever. This efficacy supplement includes results of a phase 3b, double-blind, multicenter, randomized trial (DUR001-303) that evaluated the safety and efficacy of single 1500 mg IV dalbavancin dose to two dose regimen (1000 mg on Day 1 followed by 500 mg on Day 8) for the treatment of ABSSSI. The primary endpoint for study DUR001-303 is similar to the previous studies DUR001-301 and DUR-302.

From a clinical microbiology standpoint, the sNDA is approvable pending acceptance of labeling changes to the MICROBIOLOGY subsection of the Package Insert shown below.

MICROBIOLOGY SUBSECTIONS OF THE PACKAGE INSERT
This Reviewer recommends changes to the Microbiology portion of the Package Insert as follows. Deletions are in red and strikethrough font; additions are in blue Font and double underlined.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Dalbavancin is an antibacterial drug *[see* (b) (4) *Microbiology(12.4)]*.

12.4 Microbiology

Mechanism of Action

Dalbavancin, a semisynthetic lipoglycopeptide, interferes with cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking. Dalbavancin is bactericidal *in vitro* against *Staphylococcus aureus*

(b) (4)

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antibiotic Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Tenth Edition. CLSI document M07-A10. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement. CLSI document M100-S25 Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY:

Dalbavancin is a second generation semi-synthetic lipoglycopeptide antibiotic derived from the fermentation product of *Nonomuraea* sp. It is structurally related to teicoplanin. DALVANCE™ (dalbavancin) for Injection was approved on 23 May 2014 for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive bacteria (NDA 21-883). Majority of the ABSSSI infections are caused by *Streptococcus pyogenes* and *Staphylococcus aureus* including methicillin-resistant *S. aureus*. Other *Streptococcus* species, *Enterococcus faecalis*, or Gram-negative bacteria are less frequently identified as causative agents. Dalbavancin is active against Gram-positive bacteria (*Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*) and *Enterococcus faecalis*) associated with ABSSSI. The approved adult dalbavancin dose is 1000 mg IV on Day 1 and 500 mg IV on Day 8 with dose adjustment for renally impaired patients (CRCL < 30 mg/min and not on dialysis). In this supplemental New Drug Application (sNDA) submission, the applicant has proposed an alternative dosing regimen of single dose 1500 mg IV dalbavancin for the treatment of ABSSSI caused by susceptible strains of Gram-positive bacteria.

Mechanism of Action:
Dalbavancin inhibits cell wall synthesis by binding to the terminal D-alanyl-D-alanine of the cell wall peptidoglycan and preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits.

Resistance Studies:
The resistance of Gram-positive bacteria to dalbavancin is limited to certain intrinsically glycopeptide-resistant species such as pediococci, leuconostoc and some species of lactobacilli and in bacteria expressing the *vanA* gene. The vancomycin-resistant *S. aureus* (VRSA) and vancomycin-resistant enterococci strains carry the *vanA* gene and are resistant to dalbavancin. The transfer of resistance among enterococci and to other pathogens is mediated by transposons.

***In vitro* activity:**
For testing dalbavancin, the CLSI method was standardized in 2006 with the addition of a small amount of the surfactant polysorbate-80 (P-80) to prevent adsorption of dalbavancin to plastic materials and with the use of dimethylsulfoxide (DMSO) as the intermediate diluent. The dalbavancin minimal inhibitory concentration for at least 90% of aerobic Gram-positive cocci (MIC_{90}) determined using the validated broth microdilution method ranged from ≤0.03 to 0.12 μg/mL.

The dalbavancin MICs against the MRSA and MSSA isolates ranged from ≤0.03 to 0.5 μg/mL, and ≤0.03 to 0.25 μg/mL, respectively. The dalbavancin MIC_{90} values for MRSA and MSSA isolates in the recent 2 years ranged from 0.06 to 0.12 μg/mL Approximately 0.3% of isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 μg/mL. The dalbavancin MIC distribution for *S. aureus* is unimodal and these isolates are likely wild type organisms. The dalbavancin MICs against vancomycin-intermediate (VISA) and heterogenous

vancomycin-intermediate (hVISA) *S. aureus* isolates, and teicoplanin-resistant CoNS (teicoplanin MIC>8 μg/mL) were ≤ 1μg/mL. The dalbavancin MIC_{90} against VISA was 1 μg/mL.

The dalbavancin MICs against the coagulase negative *Staphyloccus* (CoNS) isolates ranged from ≤0.03 to 1.0 μg/mL. The dalbavancin MIC_{90} values for CoNS isolates in the recent 2 years were 0.12 μg/mL. Approximately 2.3% of isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 μg/mL. However, these isolates are likely wild type organisms as the MIC distribution was unimodal.

The dalbavancin MIC_{90} for *S. pyogenes*, *S. agalactiae* and *S. dysgalactiae* were ≤0.03 μg/mL, 0.06 μg/mL, <0.03 μg/mL, respectively. Approximately 1% of *S. agalactiae* isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 μg/mL. However, these isolates are likely wild type organisms as the MIC distribution was unimodal.

The overall dalbavancin MIC_{90} against isolates of viridans group streptococci from the US was ≤ 0.06μg/mL. Approximately 0.1% of isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 μg/mL. However, these isolates are likely wild type organisms as the MIC distribution was unimodal.

In 2014, the highest dalbavancin MIC observed for *E. faecalis* isolates was 0.25 μg/mL. In the previous 3 years, the highest dalbavancin MIC observed for *E. faecalis* was >4.0 μg/mL. However, the dalbavancin MIC_{90s} for vancomycin susceptible *E. faecalis and E. faecium* were 0.12 μg/mL. The dalbavancin MIC distribution for *E. faecalis* tapers at 0.25 μg/mL and a second population appears to develop at >0.25 μg/mL. The dalbavancin MIC_{90} values for vancomycin-resistant *Enterococcus* spp isolates from US and Europe were >0.25 μg/mL.

In summary, the MIC_{90} against *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus pneumonia*, *Viridans Group Streptococci* (including *S. anginosus* group and (b) (4) and *Enterococcus faecalis* (vancomycin-susceptible isolates only) were ≤ 0.12 μg/mL in isolates from the US and Europe. The *Enterococcus faecium* (vancomycin-resistant isolates, VanA-phenotype) isolates (n = 149) from US and Europe showed dalbavancin MIC_{90} >0.25 μg/mL.

The *in vitro* bactericidal activity of dalbavancin is time-dependent. Dalbavancin is about 93% bound to plasma protein. In human, bactericidal activity of the serum was observed for dalbavancin concentration of ≥20 mg/L.

***In vivo* activity:**
Animal infection model studies in the original NDA included systemic and localized infections, in which the endpoints were survival or tissue bacterial load. The studies included serious infection models, such as staphylococcal endocarditis in rats and rabbits, in which animals were infected with MRSA and/or VISA strains, and MRSA infection in the granuloma pouch model in rats(a subcutaneous abscess model). These studies support the use of dalbavancin for treatment of infections caused by Gram-positive pathogens. PK/PD relationships were evaluated using the

neutropenic mouse thigh model. In the neutropenic mouse thigh model, area under the plasma concentration-time curve (AUC/MIC) was the PD parameter that best correlated with efficacy.

Clinical Studies:
The applicant conducted a phase 3b, double-blind, multicenter, randomized trial (DUR001-303) to evaluate the safety and efficacy of a single 1500 mg IV dalbavancin dose compared to the two dose IV dalbavancin regimen (1000 mg on Day 1 followed by 500 mg on Day 8) for the treatment of ABSSSI. Efficacy assessments included clinical assessments (evidence of systemic inflammation and infection site assessment) and microbiology (blood cultures and infection site specimen collection for pathogen identification and susceptibility testing). The primary outcome measure was clinical response, defined as a reduction of at least 20% in lesion size at 48 to 72 hours in the intent-to-treat (ITT) population. For the secondary efficacy analyses, the percentages of patients in each treatment group who demonstrated clinical success at EOT (Day 14-15 ± 2 days) or the Final Visit (Day 28 ±2 days) after the initiation of study drug were compared in the ITT, and clinically evaluable (CE) populations. The majority of baseline pathogens in this study were *S. aureus* (including methicillin-resistant *S. aureus*), *S. pyogenes* and *S. intermedius*. The clinical responders with baseline MSSA at 48-72 hours were similar in the two dalbavancin arms (89.3% in single dose arm and 89.6% in two dose arm). The single dose dalbavancin had a slightly better response in patients with baseline MRSA compared to two doses of dalbavancin (86% versus 78.7%). The response rates for *Streptococcus anginosus* group were 93.9% in the dalbavancin single dose group and 100% in the group receiving two doses. In the case of *S. pyogenes*, all 14 patients showed clinical response in the dalbavancin single dose group compared to 81.8% (18/22) in the group receiving two doses. Similar clinical success rates were observed at EOT and follow up in patients with baseline *S. aureus, Streptococcus anginosus* group, *S. pyogenes* receiving single dose or two doses of dalbavancin. Few patients had *S. dysgalactiae* as the baseline pathogens in the two treatment arms (n = 4 in single dose arm and n = 3 in the two doses arm). All patients responded clinically to treatment at 48-72 hours.

The number of patients with *Enterococcus* species in this study was small (6 patients in the single dose group compared to 11 in the two-dose group). The clinical responders with baseline *E. faecalis* at 48-72 hours were 100% (4/4) in single dose arm and 80% (8/10) in two doses arm. Only one of the two patients with *E. faecium* in the dalbavancin single dose group was a clinical responder at 48-72 hours. One patient with *E. faecium* receiving two doses of dalbavancin also was a clinical responder at 48-72 hours. Similar clinical success rates were observed at EOT and follow-up visit in these patients.

All isolates in study DUR001-303 had dalbavancin MICs of ≤0.12 μg/mL. No post-baseline isolates with increase in dalbavancin MIC (≥4 fold increase in MIC value) were observed in this study.

The dalbavancin MIC range for baseline isolates in the 3 studies ranged from 0.001 to 0.25 μg/mL. Isolates with initial dalbavancin MIC of 0.25 μg/mL were susceptible (dalbavancin MIC = 0.06 μg/mL) upon retesting. The dalbavancin MIC_{90} values for *S. aureus, S. pyogenes, S. anginosus* group and *E. faecalis* were ≤0.06 μg/mL. The MIC distribution is similar to that observed in surveillance studies.

No correlation was observed between baseline dalbavancin MIC and clinical outcome in the two treatment groups.

Determination of Breakpoints:
Susceptibility interpretive criteria (breakpoints) are proposed based on the surveillance data, PK-PD studies in the neutropenic mouse thigh infection model, human PK data, and susceptibility of baseline isolates and outcomes in the clinical trials.

The clinical trial and surveillance MIC data for *S. aureus* including methicillin resistant isolates, *S. pyogenes, S. agalactiae, S. dysgalactiae, Viridans Group Streptococci* and *E. faecalis* showed similar distributions. The dalbvancin MIC_{90} for all isolates were ≤ 0.12 μg/mL.

The clinical outcome data for isolates with dalbavancin MICs > 0.25 μg/mL were available for only two patients in the DUR001-301 and 302 studies. In DUR001-303, there were no patients with MICs ≥ 0.25 μg/mL. The MIC values for the non-susceptible isolates from studies DUR001-303, DUR001-301 and DUR001-302 isolates retested at 0.06 μg/mL. Isolates at the lower end of the MIC distribution retest to the modal MIC for the species tested. Only few (20%) of the non-susceptible isolates from surveillance studies with MICs ≥ 0.25 μg/mL remained non-susceptible when retested. Retesting of isolates at the central laboratory is useful to monitor development of resistance. Retesting of isolates at the local laboratory may be useful if it is used to guide therapy. Isolates yielding test results other than "Susceptible" should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for additional testing.

In vitro studies show that dalbavancin MIC_{90} against *S. aureus* VISA isolates is 1 μg/mL. These isolates have changes to cell wall. Also, small frequencies of sub-clones of *S. aureus* VISA isolates grew on agar containing 2 μg/mL of dalbavancin. From these studies, it appears that a dalbavancin MIC of 1-2 μg/mL may correspond with resistance development. The dalbavancin MIC_{90} for vancomycin-resistant *E. faecalis* isolates was >0.25 mg/mL in US and Europe. The ECOFF values for *S. aureus* and *Streptococcus agalactiae* published on the EUCAST website are 0.12 μg/mL.

Overall, the clinical microbiology data support a susceptible breakpoint of ≤0.12 μg/mL for *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*), *Enterococcus faecalis* (vancomycin-susceptible isolates only) based on *in vitro* MIC distributions of isolates from clinical studies and surveillance studies The non-clinical and clinical PK/PD target attainment analyses support a breakpoint of 0.25 μg/mL. Dalbavancin is not active against VanA expressing *Enterococcus* species. The dalbavancin MIC_{90} against vancomycin resistant *Enterococcus spp.* is >0.25 μg/mL in the US and Europe.

2 INTRODUCTION:

Dalbavancin is a semi-synthetic lipoglycopeptide derived from A-40926, a fermentation product of *Nonomuraea* species (Malabarba and Goldstein, 2005)[1]. It is approved for intravenous (IV) treatment of acute bacterial skin and skin structure infections (ABSSSI) in the US (2014) and in the EU (2015). The main pathogens causing ABSSSI are staphylococci and streptococci. *Enterococcus faecalis* or Gram-negative bacteria are identified as causative agents less frequently. The clinical microbiology aspects in the original application were reviewed by Dr. Peter Coderre (please see review dated February 20, 2014). Previously reviewed material is summarized along with the review of new information included in the current supplement. New information included in this submission is listed below:

1. Report 14-DUR-01: Surveillance report for 2014.
2. Report: 15-DUR-02: Retesting of Gram-positive clinical isolates included in the surveillance program for 2011 – 2013 displaying non-susceptible dalbavancin MIC results.
3. Report: 15-DUR-05: Retesting of Gram-positive clinical isolates included in the surveillance program for 2014 displaying dalbavancin MIC results at the lower end of the distribution and at the mode.
4. Report DAL-32: Study report for Etest
5. Report DAL-MC-01: In Vivo Pharmacodynamic Activity of the Glycopeptide Dalbavancin
6. Clinical study DUR001-303 Report
7. Literature:
    a. McCurdy SP, Jones RN, Mendes RE, Puttagunta S, Dunne MW. *In Vitro* Activity of Dalbavancin against Drug-Resistant *Staphylococcus aureus* Isolates from a Global Surveillance Program Antimicrob. Agents Chemother.2015; in press.

3 PRECLINICAL STUDIES:

3.1 Mechanism of Action:

Dalbavancin belongs to the glycopeptide class of antimicrobial drugs. The glycopeptide class includes the naturally occurring glycopeptides, vancomycin (Vancocin®) and teicoplanin (Targocid®, Targosid®), and the semi-synthetic derivatives, telavancin (Vibativ®) and oritavancin (Orbativ™). Dalbavancin binds to the D-alanyl-D-alanine (D-ala-D-ala) portion of the nascent peptidoglycan pentapeptide and interferes with cell wall cross-linking and synthesis in Gram-positive bacteria (Anderson 1965) (Leimkuhler 2005)[2,3]. In growing *Staphylococcus aureus* cells, dalbavancin was shown to inhibit incorporation of the peptidoglycan synthesis precursor

[1] Malabarba A, Goldstein BP. Origin, structure, and activity in vitro and in vivo of dalbavancin. J Antimicrob Chemother. 2005;55 Suppl 2:ii15-20.

[2] Anderson JS, Matsuhashi M, Haskin MA, Strominger JL. Lipidphosphoacetylmuramyl- pentapeptide and lipid-phosphodisaccharide-pentapeptide: Presumed membrane transport intermediates in cell wall synthesis. Proc Natl Acad Sci(US). 1965;53:881-9.

[3] Leimkuhler C, Chen L, Barrett D, *et al*. Differential inhibition of Staphylococcus aureus PBP2 by glycopeptide antibiotics. J Am Chem Soc. 2005;127:3250-1.

N-acetylglucosamine but had no effect on L-forms (Report GE022-04)[4]. Dalbavancin demonstrates activity against *E. faecalis* VanS strains (MIC ≤0.06 μg/mL) but not VanA strains (MICs >64 μg/mL). Using a *Bacillus subtilis lacZ* fusion strain in which the *E. faecium van*RS two-component signal transduction gene pair directs expression of *van*H-*lac*Z fusion, dalbavancin was shown to induce lacZ expression and β-galactosidase production. The study also showed that ε-aminohexanoyl-*D*-Ala-*D*-Ala was able to reverse the induction by dalbavancin, suggesting that it binds to D-alanyl-D-alanine portion of the nascent peptidoglycan. Glycopeptides (eg., dalbavancin) are generally inactive against Gram-negative organisms as they are unable to penetrate the outer membrane. No new studies relating to mechanism of action of dalbavancin were included in this submission.

3.2 Mechanism of Resistance:

No new studies relating to mechanism of resistance were included in this submission. Please see review dated February 20, 2014 by Dr. Peter Coderre for previously reviewed studies. Emergence of dalbavancin resistance has not been observed *in vitro* or *in vivo*. The resistance of Gram-positive bacteria to dalbavancin is limited to certain intrinsically glycopeptide-resistant species such as pediococci, leuconostoc, some species of lactobacilli, and in bacteria expressing the *vanA* gene. The vancomycin-resistant *S. aureus* (VRSA) strains carry the *vanA* gene and are resistant to dalbavancin.

Enterococci expressing the altered cell wall precursors can modify the stem peptide in nascent peptidoglycan and are resistant to vancomycin. Enterococci with *vanA* gene are induced by glycopeptides to produce D-alanyl-D-lactate (D-ala-D-lac) instead of D-ala-D-ala. Cross resistance of dalbavancin with vancomycin was demonstrated with a VanA strain of *Enterococcus faecium*. The susceptibility to dalbavancin was restored when the transposon encoding resistance was deleted (Report GE022-04)[3]. The transfer of resistance among enterococci and to other pathogens is mediated by transposons (eg., Tn*1546*) that are able to integrate into plasmids (Arthur 1993b)[5]. Dalbavancin is active against VanB and VanC isolates (Table 1).

[4] GE022-04. Dalbavancin inhibits cell wall biosynthesis through binding to D-Ala-D-Ala ending intermediates.

[5] Arthur M, Molinas C, Depardieu F, Courvalin P. Characterization of Tn*1546*, a Tn*3*-related transposon conferring glycopeptide resistance by synthesis of depsipeptide peptidoglycan precursors in *Enterococcus faecium* BM4147. J Bacteriol.1993b;175:117-27.

Table 1: Phenotypes Associated with the Principal Enterococcal Glycopeptide Resistance Clusters

Genotype	MIC (µg/mL) Vancomycin	Teicoplanin	Dalbavancin	Inducible by	Associated Species	Resistance Determinants
vanA	64– >1024	16–512	0.12– >32 [a]	Vancomycin, teicoplanin, others [c]	*E. faecium*, *E. faecalis*	Plasmid, Transposon
vanB	4–1024	<0.5	0.12–2 [b]	Vancomycin	*E. faecium* *E. faecalis*	Plasmid, Transposon
vanC	2–32	<0.5	0.03–0.12 [a]	Vancomycin (Also constitutive)	*E. gallinarum* *E. casseliflavus*	Chromosomal

[a] MICs for vancomycin and teicoplanin from Gold 2001.

[b] From Report DAL02M-001

[c] In a laboratory setting, it has been shown that moenomycin, bacitracin, tunicamycin, ramoplanin and glycopeptides can induce expression of the *vanA* operon (Grissom-Arnold 1997).

Resistance development by direct selection and serial passage:

Vancomycin-intermediate *S. aureus* (VISA) strains with vancomycin MICs ranging from 8-16 µg/mL have unusually thick cell walls but do not have the *vanA* gene. The dalbavancin MIC against 61 hVISA strains were ≤1 µg/mL (Report VER001-MI-004)[6] (Campanile 2010)[7]. The development of resistance to dalbavancin *in vitro* was assessed by direct selection and in serial passage experiments conducted with a number of staphylococcal isolates in 3 different laboratories (Report XRES-05062013, Report DAL02M-002, Report VER001-MI-012, Report VER001-MI-003, Lopez 2005)[8,9,10,11,12]. No increase in dalbavancin MIC was seen with a VISA strain, either in serial passage or direct plating experiments. In a study of 32 MRSA isolates, including 12 confirmed hVISA isolates, only 5 had small frequencies of sub-clones that grew on agar containing 2 µg/mL of dalbavancin (Report XRES-05062013)[8]. These same isolates showed growth on high concentrations of vancomycin. When two vancomycin susceptible strains were passaged daily for 7 days, no colonies with increased dalbavancin MIC were obtained.

Resistant strains were selected by plating 2×10^{10} colony forming units (CFU) of *S. aureus* ATCC 25923 onto Tryptic Soy agar plates containing 10 µg/mL dalbavancin, 10 µg/mL vancomycin or 15 µg/mL teicoplanin. The dalbavancin, vancomycin and teicoplanin MICs for the strain by broth microdilution were 0.06 µg/mL, 2.0 µg/mL, and 2.0 µg/mL, respectively. Plates were examined at the end of 72 hours of incubation at 35ºC. The frequencies for development of a

[6] VER001-MI-004. Activity of dalbavancin against Gram-positive organisms.

[7] Campanile F, Borbone S, Perez M, et al. Heteroresistance to glycopeptides in Italian methicillin resistant *Staphylococcus aureus* (MRSA) isolates. Int J Antimicrob Agents.2010;36:415-9.

[8] XRES-05062013. Evaluation of the potential of dalbavancin to select for reduced susceptibility in methicillin-resistant *Staphylococcus aureus*, including hVISA strains.

[9] DAL02M-002. *In vitro* microbiological characterization of dalbavancin.

[10] VER001-MI-012. Attempt to select spontaneous variants of *Staphylococcus aureus* and *Staphylococcus epidermidis* on agar media containing dalbavancin.

[11] VER001-MI-003. Serial passages of isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis* in broth media containing dalbavancin to attempt to identify resistant mutants.

[12] Lopez S, Hackbarth C, Romanò G, et al. Antistaphylococcal activity of dalbavancin, a novel glycopeptide. J Antimicrob Chemother. 2005;55 Suppl 2:ii21-4.

single step high level resistance were $<10^{-10}$ for all 3 antibiotics (Report DAL02M-002, Lopez 2005)[9,12].

A similar experiment was performed in another laboratory (Report VER001-MI-012)[10]. Five *S. aureus* strains (including 3 MRSA and one VISA), and a strain of methicillin-resistant *S. epidermidis* (MRSE) were exposed for 24 hours to various concentrations of dalbavancin and vancomycin (0.5×, 1×, 2×, 4× and 8× the MIC) in Mueller-Hinton agar. The colonies were sub-cultured on drug-free agar and MICs compared to the parent strain. For all of the colonies selected, the dalbavancin MICs were within 2-fold dilution of the MIC for the parent strain. The resistance frequencies (for both dalbavancin and vancomycin) were $<6.25\times10^{-11}$ for the 3 MRSA, $<7.25\times10^{-11}$ for the methicillin-susceptible *S. aureus* (MSSA), $<7.81\times10^{-11}$ for the VISA strain and $<1.16\times10^{-10}$ for the MRSE.

S. aureus ATCC 25923 and a clinical isolate of *S. haemolyticus* were passaged in Tryptic Soy broth at sub-MIC concentrations over 24 passages (Report DAL02M-002, Lopez 2005)[9,12]. Dalbavancin MIC values for *S. aureus* ATCC 25923 after 24 passages increased 2-fold (0.25 µg/mL to 0.5 µg/mL), while vancomycin and teicoplanin MICs increased 4- and 8-fold, respectively. In the case of the *S. haemolyticus* strain, the dalbavancin MIC increased 4-fold (from 0.12 to 0.5 µg/mL), the vancomycin MIC 2-fold, and the teicoplanin MIC 32-fold after 24 passages. Table 2 shows the MIC values obtained at baseline and after 7, 13 and 24 passages.

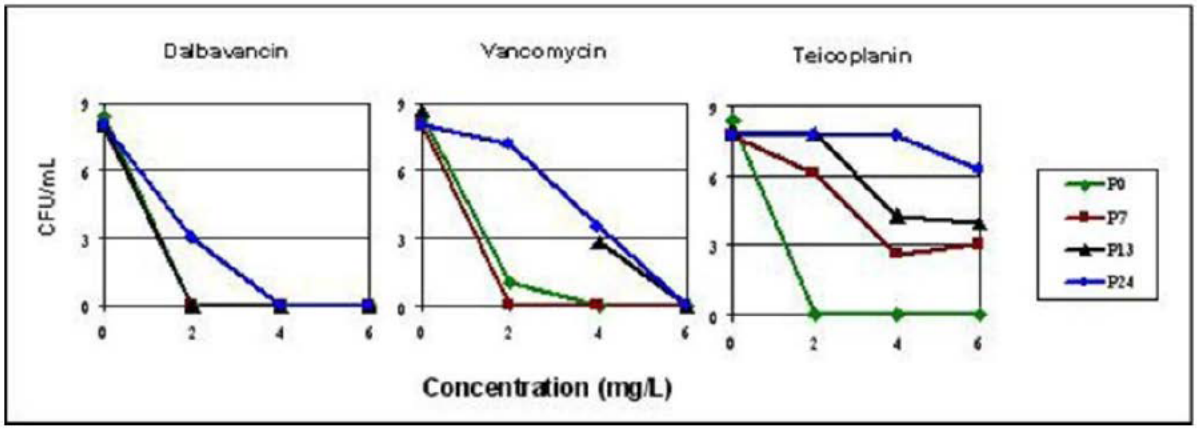
Table 2. MICs of dalbavancin, vancomycin and teicoplanin for *S. aureus* and *S.haemolyticus* after serial passage.

Strain	Passage Number	MIC (µg/mL)		
		Dalbavancin	Vancomycin	Teicoplanin
S. aureus ATCC 25923	P0	0.25	0.5	1
	P7	0.25	1	2
	P13	0.25	2	4
	P24	0.5	2	8
S. haemolyticus 4036	P0	0.12	0.5	0.5
	P7	0.12	1	2
	P13	0.12	2	8
	P24	0.5	1	16

Data from Report DAL02M-002, Lopez 2005.

Isolated colonies from these passage steps were sub-cultured and the MIC distribution in the culture was examined. For the *S. aureus* strain, the distributions for dalbavancin MICs were homogenous compared to vancomycin and teicoplanin (Figure 1). Similar results were obtained for *S. haemolyticus* subcultures (Report DAL02M-02, Lopez 2005)[9,12].

Figure 1. MIC Distributions in *S. aureus* ATCC 25923 Sub-cultured after Serial Passage



Data from Report DAL02M-002, Lopez 2005.

Six staphylococcal isolates (3 MRSA, one VISA, one MSSA and one MRSE) were passaged in cation-adjusted Mueller Hinton broth (CAMHB) containing dalbavancin or vancomycin (Report VER001 MI 003)[11]. (b) (4) Isolates with ≥ 4 fold increases in MIC were sub-cultured in triplicate on drug-free medium and the MIC values determined to confirm stability of resistant variants. Dalbavancin was active against all 6 strains of staphylococci and no resistance developed.

In conclusion, dalbavancin resistance did not arise in serial passage experiments conducted in 3 different laboratories, with staphylococcal isolates, including MRSA, VISA and methicillin-resistant coagulase negative *Staphylococcus* (CoNS). The results from the studies suggest a low potential for resistance development to dalbavancin. Although no increase in dalbavancin MIC was seen with a VISA strain, either in the serial passage or direct plating experiments, the dalbavancin MICs for hVISA strains were higher than vancomycin susceptible strains (≤ 1.0 µg/mL versus ≤ 0.12 µg/mL).

3.3 Antimicrobial Activity *In Vitro*:

For testing dalbavancin, the CLSI method was standardized in 2006 with the addition of a small amount of the surfactant polysorbate-80 (P-80) to prevent adsorption of dalbavancin to plastic materials and with the use of dimethylsulfoxide (DMSO) as the intermediate diluent. Dalbavancin is active against Gram-positive bacteria (*Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*) and *Enterococcus faecalis*) associated with ABSSSI. The dalbavancin minimal inhibitory concentration for at least 90% of aerobic Gram-positive cocci (MIC_{90}) determined using the validated broth microdilution method ranged from ≤0.03 to 0.12 µg/mL. The dalbavancin MICs against vancomycin-intermediate (VISA) and heterogenous vancomycin-intermediate (hVISA) *S. aureus* isolates, and teicoplanin-resistant CoNS (teicoplanin MIC>8 µg/mL) were ≤ 1µg/mL (Campanile 2010; Citron 2014; Report XRES

05062013; Report VER001-MI-004, SENTRY Database, Report 14-DUR-01, McCurdy SP, 2015)[7,13,8,6,14,15,16]. Data for each pathogen is reviewed below.

S. aureus:

The MIC distributions, by year, for a total of over 50,000 *S. aureus* isolates (methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA)) from the US are presented in Tables 3 and 4 from the SENTRY Study.

Table 3. Thirteen -Year (2002-2014) Surveillance Trends in Dalbavancin MICs against Methicillin-Susceptible *S. aureus* from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (986)	298	663	23	2	--	0.06	0.06
2003 (843)	402	428	12	1	--	0.06	0.06
2004 (1232)	558	653	20	1	--	0.06	0.06
2005 (1765)	670	1042	53	--	--	0.06	0.06
2006 (2506)	934	1464	103	5	--	0.06	0.06
2007 (2711)	371	2038	294	8	--	0.06	0.12
2008 (2411)	256	1780	363	12	--	0.06	0.12
2009 (2441)	249	1855	312	25	--	0.06	0.12
2010 (3025)	1211	1707	99	8	--	0.06	0.06
2011 (1976)	785	1117	75	--	--	0.06	0.06
2012 (1943)[a]	385	1349	208	1	--	0.06	0.06
2013 (1953)	461	1238	246	8	--	0.06	0.12
2014 (875)	423	434	18	--	--	0.06	0.06
All (24,677)	7004 (28.4)[a]	15,774 (63.9)[a]	1826 (7.4)[a]	63 (0.3)[a]	--	0.06	0.06

[a] Percentage of all strains in parenthesis.

Data from (b) (4) JMI Laboratories, SENTRY database.

[13] Citron DM, Tyrrell KL, Goldstein EC, Comparative in vitro activities of dalbavancin and seven comparator agents against 41 Staphylococcus species cultured from osteomyelitisinfections and 18 VISA and hVISA strains Diag Infect Dis.79 (2014) 438-440

[14] (b) (4) 2013 Tables from SENTRY database.

[15] 14-DUR-01 Dalbavancin International (Two Continent) Surveillance Report for 2014

[16] McCurdy SP, Jones RN, Mendes RE, Puttagunta S, Dunne MW In Vitro Activity of Dalbavancin against Drug-Resistant *Staphylococcus aureus* Isolates from a Global Surveillance Program Antimicrob. Agents Chemother.2015; in press

Table 4. Thirteen -Year (2002-2014) Surveillance Trends in Dalbavancin MICs against Methicillin-Resistant *S. aureus* from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (831)	281	531	16	2	1	0.06	0.06
2003 (483)	244	227	11	1	--	≤0.03	0.06
2004 (1210)	537	648	22	2	1	0.06	0.06
2005 (1853)	699	1085	66	3	--	0.06	0.06
2006 (3207)	1140	1945	113	8	1	0.06	0.06
2007 (3400)	448	2625	318	9	--	0.06	0.06
2008 (3199)	263	2438	472	26	--	0.06	0.12
2009 (2549)	255	1920	348	26	--	0.06	0.12
2010 (3136)	1143	1885	96	12	--	0.06	0.06
2011 (1931	700	1169	60	--	2	0.06	0.06
2012 (1722)	269	1235	216	--	2	0.06	0.12
2013 (1947)	475	1258	212	3		0.06	0.12
2014 (750)	364	383	3	--	--	0.06	0.06
All (26,218)	6818 (26.0)[a]	17,349 (66.2)[a]	1,953(7.4)[a]	90 (0.35)[a]	7 (0.03)[a]	0.06	0.06

[a] Percentage of all strains in parenthesis.
Data from (b) (4) JMI Laboratories, SENTRY database.

Reviewer comment:
The dalbavancin MICs against the MRSA and MSSA isolates ranged from ≤0.03 to 0.5 µg/mL, and ≤0.03 to 0.25 µg/mL, respectively. The dalbavancin MIC_{90} values for MRSA and MSSA isolates in the recent 2 years ranged from 0.06 to 0.12 µg/mL Approximately 0.3% of isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 µg/mL. However, these isolates may be wild type as the dalbavancin MIC distribution for *S. aureus* was unimodal.

Coagulase Negative *Staphylococcus* (CoNS):
Surveillance data for 8,248 CoNS isolates were collected during the 13-year period 2002-2014 (Table 5). The dalbavancin MIC_{90}s against CoNS were 0.12 µg/mL.

Table 5. Thirteen -Year (2002-2014) Surveillance Trends in Dalbavancin MICs against Coagulase-Negative Staphylococci from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)						MIC	
	≤0.03	0.06	0.12	0.25	0.5	1	50%	90%
2002 (335)	270	42	16	7	--	--	≤0.03	0.06
2003 (301)	208	66	18	6	3	--	≤0.03	0.06
2004 (305)	199	75	20	7	3	1	≤0.03	0.12
2005 (419)	272	113	25	6	2	1	≤0.03	0.06
2006 (1115)	662	350	77	23	2	1	≤0.03	0.06
2007 (1297)	482	613	167	32	2	1	0.06	0.12
2008 (1219)	387	604	189	36	3	--	0.06	0.12
2009 (1007)	313	510	157	22	4	1	0.06	0.12
2010 (1018)	612	328	74	3	1	--	≤0.03	0.06
2011 (287)	165	91	27	4	--	--	≤0.03	0.12
2012 (272)	134	105	25	7	1	--	0.06	0.12
2013 (315)	117	145	43	8	2	--	0.06	0.12
2014 (358)	158	148	40	12	--	--	0.06	0.12
All (8,248)	3,979 (48.2)[a]	3,190 (38.7)[a]	878 (10.6)[a]	173 (2.1)[a]	23 (0.3)[a]	5 (<0.1)[a]	0.06	0.12

[a] Percentage of all strains in parenthesis. Data from (b) (4) JMI Laboratories, SENTRY database.

Reviewer comment:

The dalbavancin MICs against the CoNS isolates ranged from ≤0.03 to 1.0 µg/mL. The dalbavancin MIC_{90} values for CoNS isolates in the recent 2 years were 0.12 µg/mL. Approximately 2.3% of isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 µg/mL. However, the dalbavancin MIC distribution for CoNS was unimodal.

β-hemolytic *Streptococci*: The *in vitro* susceptibility data for *S. pyogenes* (N=2,590), *S. agalactiae* (N=3,287) and *S. dysgalactiae* (N=132) isolates from the US are presented in Tables 6, 7 and 8 respectively. The dalbavancin MIC_{90} for *S. pyogenes*, *S. agalactiae* and *S. dysgalactiae* were ≤0.03 µg/mL, 0.06 µg/mL, <0.03 µg/mL, respectively.

Table 6. Thirteen -Year (2002-2014) Surveillance Trends in Dalbavancin MICs against *S. pyogenes* from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (31)	30	0	1	--	--	≤0.03	≤0.03
2003 (44)	44	--	--	--	--	≤0.03	≤0.03
2004 (95)	93	2	--	--	--	≤0.03	≤0.03
2005 (141)	141	--	--	--	--	≤0.03	≤0.03
2006 (225)	222	2	1	--	--	≤0.03	≤0.03
2007 (217)	214	3	--	--	--	≤0.03	≤0.03
2008 (187)	185	2	--	--	--	≤0.03	≤0.03
2009 (327)	317	10	--	--	--	≤0.03	≤0.03
2010 (478)	465	12	1	--	--	≤0.03	≤0.03
2011 (266)	249	15	2	--	--	≤0.03	≤0.03
2012 (222)	211	9	2	--	--	≤0.03	≤0.03
2013 (249)	230	17	2	--	--	≤0.03	≤0.03
2014 (108)	107	1	--	--	--	0.008	0.03
All (2,590)	2,508 (96.8)[a]	73 (2.8)[a]	9 (0.3)[a]	--	--	≤0.03	≤0.03

[a] Percentage of all strains in parenthesis.

Data from (b) (4) JMI Laboratories, SENTRY database.

Table 7. Thirteen -Year (2002-2014) Surveillance Trends in Dalbavancin MICs against *S. agalactiae* from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (61)	48	7	6	--	--	≤0.03	0.06
2003 (69)	63	5	1	--	--	≤0.03	≤0.03
2004 (118)	100	17	1	--	--	≤0.03	0.06
2005 (157)	151	4	0	2	--	≤0.03	≤0.03
2006 (275)	253	17	3	2	--	≤0.03	≤0.03
2007 (286)	258	25	3	--	--	≤0.03	≤0.03
2008 (238)	219	15	4	--	--	≤0.03	≤0.03
2009 (485)	382	68	28	7	--	≤0.03	0.06
2010 (724)	572	95	35	22	--	≤0.03	0.06
2011 (255)	160	65	30	0	--	≤0.03	0.12
2012 (245)	215	22	8	0	--	≤0.03	0.06
2013 (262)	253	9	--	--	--	≤0.03	≤0.03
2014 (112)	110	2	--	--	--	0.015	0.03
All (3,287)	2,784 (84.7)[a]	351 (10.7)[a]	119 (3.6)[a]	33 (1.0)[a]	--	≤0.03	0.06

[a] Percentage of all strains in parenthesis.

Data from (b) (4) JMI Laboratories, SENTRY database.

Table 8. Three Year 2012-2014 Surveillance Trends in Dalbavancin MICs against *S.dysgalactiae* from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2012 (7)	4	3	--	--	--	≤0.03	--
2013 (50.0)	41	8	1			≤0.03	0.06
2014 (75)	68	5	2	--	--	0.015	0.03
All (132)	113 (86.3)[a]	16 (11.5)[a]	3(2.3)[a]	--	--	≤0.03	0.06

[a] Percentage of all strains in parenthesis.

Data from (b) (4) JMI Laboratories, SENTRY database.

Reviewer comment:

The dalbavancin MIC_{90} for *S. pyogenes*, *S. agalactiae* and *S. dysgalactiae* were ≤0.03 µg/mL, 0.06 µg/mL, <0.03 µg/mL, respectively. Approximately 1% of *S. agalactiae* isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 µg/mL. However, the dalbavancin MIC distribution for *S. pyogenes*, *S. agalactiae* and *S. dysgalactiae* was unimodal.

Viridans Group Streptococci:

The overall dalbavancin MIC_{90} against 2984 isolates of viridans group streptococci from the US over 13 years was ≤ 0.06 µg/mL (Table 9). Approximately 0.1% of isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 µg/mL. However, the dalbavancin MIC distribution for viridans group streptococci was unimodal.

Table 9. Thirteen -Year (2002-2014) Surveillance Trends in Dalbavancin MICs against Viridans Group Streptococci from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (33)	33	--	--	--	--	≤0.03	≤0.03
2003 (47)	47	--	--	--	--	≤0.03	≤0.03
2004 (63)	60	3	--	--	--	≤0.03	≤0.03
2005 (92)	90	1	1	--	--	≤0.03	≤0.03
2006 (256)	242	10	4	--	--	≤0.03	≤0.03
2007 (304)	274	26	4	--	--	≤0.03	≤0.03
2008 (228)	196	29	3	--	--	≤0.03	0.06
2009 (323)	269	47	6	1	--	≤0.03	0.06
2010 (628)	563	59	4	2	--	≤0.03	0.06
2011 (240)	216	22	2	--	--	≤0.03	≤0.03
2012 (264)	237	26	1	--	--	≤0.03	0.06
2013 (286)	263	20	3	--	--	≤0.03	≤0.03
2014 (220)	203	16	1	--	--	0.015	0.03
All (2,984)	2,693 (90.2)[a]	259 (8.7)[a]	29 (1.0)[a]	3 (0.1)[a]	--	≤0.03	≤0.03

[a] Percentage of all strains in parenthesis.
Data from (b) (4) JMI Laboratories, SENTRY database.

Streptococcus pneumoniae:

The dalbavancin MIC_{90} against 13,209 *S. pneumoniae* isolates in the last 13 years was ≤0.03 µg/mL (Table 10). Less than 0.1% of isolates had MIC values greater than the current dalbavancin breakpoint of ≤ 0.12 µg/mL. However, the dalbavancin MIC distribution for *S. pneumoniae* was unimodal.

Table 10. Thirteen-Year (2002-2014) Surveillance Trends in Dalbavancin Potency against *S. pneumoniae* from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (440)	434	6	--	--	--	≤0.03	≤0.03
2003 (278)	277	1	--	--	--	≤0.03	≤0.03
2004 (686)	679	6	0	1	--	≤0.03	≤0.03
2005 (1206)	1192	13	0	1	--	≤0.03	≤0.03
2006 (1250)	1246	4	--	--	--	≤0.03	≤0.03
2007 (1241)	1171	70	--	--	--	≤0.03	≤0.03
2008 (1209)	1169	40	--	--	--	≤0.03	≤0.03
2009 (1408)	1297	109	2	--	--	≤0.03	≤0.03
2010 (1785)	1754	30	1	--	--	≤0.03	≤0.03
2011 (1408)	1368	40	--	--	--	≤0.03	≤0.03
2012 (876)	848	28	--	--	--	≤0.03	≤0.03
2013 (1072)	1057	14	1	--	--	≤0.03	≤0.03
2014 (350)	343	7	--	--	--	0.015	0.03
All (13,209)	12,835 (97.2)[a]	368 (2.8)[a]	4 (<0.1)[a]	2 (<0.1)	--	≤0.03	≤0.03

[a] Percentage of all strains in parenthesis.
Data from (b) (4) JMI Laboratories, SENTRY database.

Enterococcus:

The dalbavancin MIC distributions for 8,802 *E. faecalis* US isolates are presented in Table 11. The MIC_{50} and MIC_{90} of dalbavancin against *E. faecalis* were 0.06 and 0.12 µg/mL, respectively. The overall dalbavancin MIC distributions (2002-2010) for US isolates of vancomycin-susceptible *E. faecium*, vancomycin-resistant *E. faecium* and vancomycin-resistant *E. faecalis* are presented in Table 12.

Table 11 Thirteen -Year (2002-2014) Surveillance Trends in Dalbavancin MIC against *E. faecalis* from the USA (appended from submission).

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)								MIC	
	≤0.03	0.06	0.12	0.25	0.5	1	2	≥4	50%	90%
2002 (359)	269	83	2	1	0	0	0	4	≤0.03	0.06
2003 (602)	329	208	22	0	1	2	4	36	≤0.03	0.12
2004 (534)	276	238	10	0	2	1	1	6	≤0.03	0.06
2005 (816)	429	340	22	3	1	0	1	20	≤0.03	0.06
2006 (1028)	525	422	40	1	0	0	0	40	≤0.03	0.06
2007 (1041)	369	570	59	3	0	0	1	39	0.06	0.06
2008 (944)	233	560	94	7	0	0	0	50	0.06	0.12
2009 (959)	257	568	92	10	1	1	0	30	0.06	0.12
2010 (1173)	509	560	61	3	0	1	1	38	0.06	0.06
2011(444)	148	240	30	7	0	0	0	1	0.06	0.12
2012 (297)	23	185	73	6	1	0	0	9	0.06	0.12
2013 (354)	81	188	73	1	0	0	1	10	0.06	0.12
2014 (251)	21	211	13	6[b]	--	--	--	--	0.06	0.06
All (8,802)	3,469 (39.4)[a]	4,373 (49.7)[a]	591 (6.7)[a]	48 (0.54)[a]	6 (<0.1)[a]	5 (<0.1)[a]	9 (0.1)[a]	283 (3.2)	0.06	0.12

[a] Percentage of all strains in parenthesis.

[b] Highest dose tested

Data from (b) (4) JMI Laboratories, SENTRY database.

Table 12 Summary of Nine-Year (2002-2010) Surveillance Data for Dalbavancin Potency against Vancomycin-Susceptible and Vancomycin -Resistant *E. faecium* and Vancomycin-Resistant *E. faecalis* isolates from the US (appended from submission).

Organism (No. Tested 2002-2012)	No. Occurrences at Dalbavancin MIC (µg/mL)								MIC	
	≤0.03	0.06	0.12	0.25	0.5	1	2	≥4	50%	90%
E. faecium VanS (961)	185 (19.3)[a]	395 (41.1)	332 (34.5)	41 (4.3)	1 (0.1)	3 (0.3)	1 (0.1)	3 (0.3)	0.06	0.12
E. faecium VanR (3029)	34 (1.1)	38 (1.2)	54 (1.8)	95 (3.1)	110 (3.6)	136 (4.5)	178 (5.9)	2,384 (78.7)	≥4	≥4
E. faecalis VanR (347)	8 (2.3)	21 (6.1)	37 (10.7)	2 (0.6)	4 (1.2)	4 (1.2)	8 (2.3)	263 (75.8)	≥4	≥4

Abbreviations: VanS=Vancomycin-susceptible; VanR=Vancomycin-resistant.

[a] Percentage of all strains in parenthesis.

Data from (b) (4) JMI Laboratories, SENTRY database.

Reviewer Comments:

For 2014 surveillance, the highest dalbavancin MIC observed for *E. faecalis* isolates was 0.25 µg/mL. In the previous 3 years, the highest dalbavancin MIC observed for *E. faecalis* was >4.0 µg/mL. However, the dalbavancin MIC_{90s} for vancomycin susceptible *E. faecalis and E. faecium* were 0.12 µg/mL while the MIC_{90} against vancomycin resistant *E. faecalis* and *E. faecium* were ≥ 4.0 µg/mL. Thus, dalbavancin MIC distribution for *Enterococcus* species is bimodal. There appears to be a correlation between dalbavancin MIC values of ≥2 µg/mL and VanA expression based on the overall MIC distribution for *E. faecalis* and *E. faecium* isolates.

US versus EU isolates:

Dalbavancin MIC_{90} values were ≤0.12 µg/mL for all groups of staphylococci and streptococci, and vancomycin-susceptible *Enterococcus* isolates in both geographic regions (Table 13). The dalbavancin MIC_{90} values for vancomycin-resistant *Enterococcus* spp isolates were >0.25 µg/mL.

Table 13 Dalbavancin susceptibility of key pathogens collected in European Hospitals from 2011 to 2014.

	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
Organism (N)	**≤0.03**	**0.06**	**0.12**	**0.25**	**>0.25**	**50%**	**90%**
S. aureus (10,654)	3627	6,256	760	11	0	0.06	0.06
MRSA (2809)	1098	1548	157	6	0	0.06	0.06
MSSA (7845)	2529	4708	603	5	0	0.06	0.06
β-hemolytic streptococci (2044)	1827	165	39	13	0	≤0.03	0.06
S. pyogenes (936)	875	55	6	0	0	≤0.03	≤0.03
S. agalactiae (683)	578	63	29	13	0	≤0.03	0.06
Viridans streptococci (1052)	911	131	10	0	0	≤0.03	0.06
Enterococcus spp. (2961)	567	1527	494	69	304	0.06	>0.25
Van-S (2514)	542	1465	460	45	2	0.06	0.12
Van-NS (399)	14	36	24	23	302	>0.25	>0.25

Data from (b) (4) Sentry database; Van-S=vancomycin susceptible Van-NS=vancomycin non-susceptible

The 2014 Surveillance Report:

The 2014 Dalbavancin International Surveillance conducted as part of the SENTRY program[17] also showed dalbavancin MIC_{90} of 0.06 µg/mL for MRSA (n =1, 166) and MSSA(n =2,084) in the US and Europe. Among species of CoNS with >10 isolates each, dalbavancin MIC_{90} values were 0.03 µg/mL for *S. capitis* (n =41), 0.06 µg/mL for *S. hominis* (68), *S. lugdunensis* (60) and *S.simulans* (n =14). The dalbavancin MIC_{90} of 0.12 µg/ml were obtained for *S. epidermidis* (n=438) and *S. warneri* (n =22). *S. haemolyticus* (n =72) and *S. saprophyticus* (n =22) showed dalbavancin MIC_{90} values of 0.25 µg/ml. The dalbavancin MIC_{90} for CoNS were 2 fold higher for isolates collected in Europe (0.12 µg/ml) versus US (0.06 µg/mL). Against *S. pneumoniae* (n = 698, includes 254 penicillin-resistant *S. pneumoniae* (PRSP)), the dalbavancin MIC_{90} values were 0.03µg/mL. Similar results were observed for β-hemolytic streptococci (Table 14). The dalbavancin MIC_{90} for the *S. anginosus* group for the two regions were 0.015 µg/mL while the

[17] 14-DUR-01 Dalbavancin International (two continents) Surveillance Report for 2014

dalbavancin MIC_{90} for other species including 160 (b) (4) *S. oralis* isolates were 0.06 µg/mL (Table 15).

Table 14. Antimicrobial activity of dalbavancin against β-hemolytic streptococci submitted to the 2014 Dalbavancin International Surveillance as part of the SENTRY Program.

Region	MIC (µg/ml)		Number (cumulative %) of isolates inhibited at each dalbavancin MIC (µg/ml)						
Species (number tested)	50%	90%	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12
Overall (594)	0.015	0.03	2 (0.3)	32 (5.7)	154 (31.6)	283 (79.3)	104 (96.8)	15 (99.3)	4 (100.0)
S. pyogenes (214)	0.008	0.03	1 (0.5)	25 (12.1)	86 (52.3)	70 (85.0)	27 (97.7)	4 (99.5)	1 (100.0)
S. agalactiae (210)	0.015	0.03	0 (0.0)	2 (1.0)	12 (6.7)	152 (79.0)	41 (98.6)	3 (100.0)	
S. dysgalactiae (170)	0.015	0.03	1 (0.6)	5 (3.6)	56 (36.7)	61 (72.2)	36 (93.5)	8 (98.2)	3 (100.0)
USA (296)	0.015	0.03	1 (0.3)	14 (5.1)	71 (29.1)	153 (80.7)	47 (96.6)	8 (99.3)	2 (100.0)
S. pyogenes (108)	0.008	0.03	1 (0.9)	12 (12.0)	44 (52.8)	38 (88.0)	12 (99.1)	1 (100.0)	
S. agalactiae (112)	0.015	0.03	0 (0.0)	1 (0.9)	3 (3.6)	83 (77.7)	23 (98.2)	2 (100.0)	
S. dysgalactiae (76)	0.015	0.03	0 (0.0)	1 (1.3)	24 (33.3)	32 (74.7)	12 (90.7)	5 (97.3)	2 (100.0)
Europe (298)	0.015	0.03	1 (0.3)	18 (6.4)	83 (34.2)	130 (77.9)	57 (97.0)	7 (99.3)	2 (100.0)
S. pyogenes (106)	0.008	0.03	0 (0.0)	13 (12.3)	42 (51.9)	32 (82.1)	15 (96.2)	3 (99.1)	1 (100.0)
S. agalactiae (98)	0.015	0.03	0 (0.0)	1 (1.0)	9 (10.2)	69 (80.6)	18 (99.0)	1 (100.0)	
S. dysgalactiae (94)	0.015	0.03	1 (1.1)	4 (5.3)	32 (39.4)	29 (70.2)	24 (95.7)	3 (98.9)	1 (100.0)

Table 15. Antimicrobial activity of dalbavancin against viridans group streptococci submitted to the 2014 Dalbavancin International Surveillance as part of the SENTRY Program.

Region	MIC (µg/ml)		Number (cumulative %) of isolates inhibited at each dalbavancin MIC (µg/ml)						
Group (number tested)	50%	90%	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12
Overall[a] (435)	0.015	0.03	14 (3.2)	45 (13.6)	81 (32.2)	144 (65.3)	113 (91.3)	35 (99.3)	3 (100.0)
Penicillin-susceptible[b] (332)	0.015	0.03	12 (3.6)	41 (16.0)	64 (35.2)	98 (64.8)	86 (90.7)	28 (99.1)	3 (100.0)
Penicillin-non-susceptible[c] (103)	0.015	0.03	2 (1.9)	4 (5.8)	17 (22.3)	46 (67.0)	27 (93.2)	7 (100.0)	
S. anginosus group[d] (136)	0.008	0.015	13 (9.6)	34 (34.6)	48 (69.9)	35 (95.6)	4 (98.5)	2 (100.0)	
Other species[e] (299)	0.015	0.06	1 (0.3)	11 (4.0)	33 (15.1)	109 (51.5)	109 (88.0)	33 (99.0)	3 (100.0)
USA (220)	0.015	0.03	5 (2.3)	27 (14.5)	38 (31.8)	76 (66.4)	57 (92.3)	16 (99.5)	1 (100.0)
Penicillin-susceptible (174)	0.015	0.03	5 (2.9)	24 (16.7)	30 (33.9)	58 (67.2)	42 (91.4)	14 (99.4)	1 (100.0)
Penicillin-non-susceptible (46)	0.015	0.03	0 (0.0)	3 (6.5)	8 (23.9)	18 (63.0)	15 (95.7)	2 (100.0)	
S. anginosus group (75)	0.008	0.015	5 (6.7)	22 (36.0)	24 (68.0)	21 (96.0)	3 (100.0)		
Other species (145)	0.015	0.06	0 (0.0)	5 (3.4)	14 (13.1)	55 (51.0)	54 (88.3)	16 (99.3)	1 (100.0)
Europe (215)	0.015	0.03	9 (4.2)	18 (12.6)	43 (32.6)	68 (64.2)	56 (90.2)	19 (99.1)	2 (100.0)
Penicillin-susceptible (158)	0.015	0.06	7 (4.4)	17 (15.2)	34 (36.7)	40 (62.0)	44 (89.9)	14 (98.7)	2 (100.0)
Penicillin-non-susceptible (57)	0.015	0.03	2 (3.5)	1 (5.3)	9 (21.1)	28 (70.2)	12 (91.2)	5 (100.0)	
S. anginosus group (61)	0.008	0.015	8 (13.1)	12 (32.8)	24 (72.1)	14 (95.1)	1 (96.7)	2 (100.0)	
Other species (154)	0.015	0.06	1 (0.6)	6 (4.5)	19 (16.9)	54 (51.9)	55 (87.7)	17 (98.7)	2 (100.0)

a Includes *S. anginosus* (80 strains), *S. anginosus* group (13 strains), *S. australis* (8 strains), *S. bovis* group (2 strains), *S. canis* (6 strains), *S. constellatus* (33 strains), *S. cristatus* (4 strains), *S. gallolyticus* (16 strains), *S. gordonii* (15 strains), *S. infantis* (5 strains), *S. intermedius* (10 strains), (b) (4) *oralis* (160 strains),*S. mutans* (2 strains), *S. parasanguinis* (24 strains), *S. salivarius*/*vestibularis* (41 strains), *S. sanguinis* (14 strains), *S. sobrinus* (1 strain), and *S. suis* (1 strain).
b Isolates exhibiting penicillin MIC results of ≤0.12 µg/ml.
c Isolates exhibiting penicillin MIC results of >0.12 µg/ml.
d Includes *S. anginosus* group (13 strains), *S. anginosus* (80 strains), *S. constellatus* (33 strains) and *S. intermedius* (10 strains).
e Includes *S. australis* (8 strains), *S. bovis* group (2 strains), *S. canis* (6 strains), *S. cristatus* (4 strains), *S. gallolyticus* (16 strains), *S. gordonii* (15 strains), *S.infantis* (5 strains), (b) (4) *oralis* (160 strains), *S. mutans* (2 strains), *S. parasanguinis* (24 strains), *S. salivarius*/*vestibularis* group (41 strains), *S. sanguinis* (14 strains), *S. sobrinus* (1 strain), and *S. suis* (1 strain).

Reviewer comment:
In summary, the dalbavancin MIC_{90} against *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae*, *Streptococcus dysgalactiae, Streptococcus pneumonia, Viridans Group Streptococci* (including *S. anginosus* group), and *Enterococcus faecalis* (vancomycin-susceptible isolates only) were ≤ 0.12 µg/mL. The *Enterococcus faecium* (vancomycin-resistant isolates, VanA-phenotype) isolates (n = 149) showed dalbavancin MIC_{90} >0.25 µg/mL.

Retesting of surveillance isolates:
The applicant submitted two studies (15-DUR-02 and 15-DUR-05) that retested dalbavancin MICs against gram-positive clinical isolates from the surveillance program. In study 15-DUR-02, isolates of *S. aureus* and *Streptococcus* were retested to confirm the dalbavancin non-susceptible results obtained in the surveillance program during 2011 – 2013 after the FDA approved dalbavancin with susceptible MIC interpretive criteria of ≤0.12 µg/mL. A small percent of isolates (0.18%) in the SENTRY Surveillance study exhibited dalbavancin MIC > 0.12 µg/mL. These isolates included *S. aureus* (40 among a total of 20,496 clinical isolates), Group G *Streptococcus* (one among a total of 3,451 β-haemolyticus streptococci), *S. agalactiae* (38 among a total of 3,451 β-haemolyticus streptococci). The testing was performed using the broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI; M07-A10; 2015). (b) (4) . For the testing of streptococci, Cation-adjusted Mueller-Hinton Broth supplemented with 2.5 - 5% lysed horse blood was used. QC strains (*S. aureus* ATCC 29213, *Streptococcus pneumoniae* ATCC 49619) were included in the testing.

The initial dalbavancin MIC against *S. aureus* isolates selected for retesting was 0.25 µg/ml, except for four isolates with MICs of 0.5 µg/ml. Among those isolates, only 20.5% (8/39) showed reproducible non-susceptible MIC results (i.e. ≥0.25 µg/ml; Table 16). The majority (79.5%; 31/39) of selected isolates had dalbavancin MIC results of 0.03 – 0.12 µg/ml (2 isolates at 0.03 µg/ml; 24 isolates at 0.06 µg/ml; and 5 isolates at 0.12 µg/ml). Only one isolate showed vancomycin MIC results considered significantly different between tests (i.e. ≤0.12 and 1 µg/ml; Table 16). In one isolate the bacterial identification didn't match (initially *S. aureus*, retested isolate *S. haemolyticus*).

The initial dalbavancin MIC for all streptococci isolates was 0.25 µg/mL. The dalbavancin MIC was not reproducible against these isolates. The dalbavancin MIC after retesting were as follows: 32 isolates at 0.015 µg/ml; 5 isolates at 0.03 µg/ml; and 2 isolates at 0.06 µg/ml (Table 17).

Table 16. Initial and final (upon retesting) MIC values obtained for dalbavancin when tested against selected non-susceptible *S. aureus* surveillance isolates.

		MIC (μg/ml)[a]			
Collection No	Year	DAL (initial)	DAL (final)	VAN (initial)	VAN (final)
765407	2013	0.25	0.03	1	1
765494	2013	0.25	0.03	0.5	0.5
640319	2012	0.25	0.06	1	1
645660	2012	0.25	0.06	1	1
645661	2012	0.25	0.06	1	1
645662	2012	0.25	0.06	1	1
645668	2012	0.25	0.06	1	1
645674	2012	0.25	0.06	1	1
645692	2012	0.25	0.06	1	1
645872	2012	0.25	0.06	1	1
650678	2012	0.25	0.06	2	2
655398	2011	0.25	0.06	1	1
657918	2011	0.25	0.06	≤0.12	1
659633	2011	0.25	0.06	1	1
688842	2011	0.25	0.06	2	1
689064	2011	0.25	0.06	1	1
712070	2012	0.25	0.06	1	1
765480	2013	0.25	0.06	1	1
765481	2013	0.25	0.06	1	1
765482	2013	0.25	0.06	1	1
765483	2013	0.25	0.06	1	1
765496	2013	0.25	0.06	1	1
765502	2013	0.25	0.06	1	1
771114	2013	0.25	0.06	1	1
775901	2013	0.25	0.06	1	1
781926	2013	0.25	0.06	1	1
640328	2012	0.25	0.12	2	2
706580	2011	0.25	0.12	1	1
708843	2012	0.25	0.12	1	2
718131	2012	0.25	0.12	2	2
744073	2013	0.25	0.12	2	2
652091	2012	0.25	0.25	2	2
702743[b]	2011	0.25	0.25[b]	1	1
712083	2012	0.25	0.25	2	1
738619	2013	0.25	0.25	2	2
639378	2012	0.5	>0.25	4	4
700634	2011	0.5	>0.25	2	2
700635	2011	0.5	>0.25	2	2
725997	2012	0.5	>0.25	2	2
810332	2013	0.25	>0.25	2	2

a. DAL = dalbavancin; VAN = vancomycin.
b. Bacterial identification confirmed as *S. haemolyticus*.

Table 17. Initial and final (upon retesting) MIC values obtained for dalbavancin when tested against selected non-susceptible streptococcal surveillance isolates.

			MIC (μg/ml)[a]			
CollectionNo	Organism	Year	DAL (initial)	DAL (final)	VAN (initial)	VAN (final)
632794	*S. agalactiae*	2012	0.25	0.015	0.5	0.25
640944	*S. agalactiae*	2012	0.25	0.015	0.5	0.5
655433	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
655796	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
655797	*S. agalactiae*	2011	0.25	0.015	1	0.5
655865	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
655945	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
656593	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
656886	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
657087	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
657380	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
657647	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
658011	*S. agalactiae*	2011	0.25	0.015	0.25	0.25
659407	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
659526	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
659903	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
672271	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
673642	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
675996	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
677090	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
677493	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
677499	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
678903	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
684068	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
684076	*S. agalactiae*	2011	0.25	0.015	1	0.5
689701	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
695307	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
695309	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
695311	*S. agalactiae*	2011	0.25	0.015	1	0.5
695427	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
695738	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
705745	*S. agalactiae*	2011	0.25	0.015	0.5	0.5
668347	*S. agalactiae*	2011	0.25	0.03	0.5	0.5
675136	*S. agalactiae*	2011	0.25	0.03	0.5	0.5
675138	*S. agalactiae*	2011	0.25	0.03	0.5	0.5
696722	*S. agalactiae*	2011	0.25	0.03	0.5	0.5
701376	*S. agalactiae*	2011	0.25	0.03	0.5	0.5
657983	*S. agalactiae*	2011	0.25	0.06	0.5	0.5
715077	*S. dysgalactiae*[b]	2012	0.25	0.06	0.25	0.25

a. DAL = dalbavancin; VAN = vancomycin.
b. Isolates initially identified as streptococcus of Group G.

In the study 15-DUR-05, dalbavancin MIC was retested for isolates at the lower end of the MIC distribution in the 2014 surveillance program. The following isolates were included in this study: (a) *Staphylococcus aureus*: (10 isolates with initial dalbavancin MIC values ranging between 0.004 and 0.06 μg/ml), and (b) β-hemolytic streptococci: *Streptococcus agalactiae* (7 isolates with initial dalbavancin MIC values ranging between 0.004 and 0.015 μg/ml); *Streptococcus dysgalactiae* (one isolate with dalbavancin MIC ≤0.002 μg/ml) and two *Streptococcus pyogenes* (2 isolates with initial dalbavancin MIC of ≤0.002 and 0.004 μg/ml),

All isolates displaying initial MIC values at the lower end of the MIC distribution had MICs closer to the respective modal MIC upon retesting with the exception of *S. pyogenes* 830142,

which showed consistent MIC values at ≤0.002 μg/ml (Table 18). All *S. aureus* and *S. agalactiae* isolates exhibiting initial MIC values at the respective mode (i.e. 0.03 – 0.06 and 0.015 μg/ml, respectively) showed reproducible MIC (± one doubling dilution) upon retesting.

Table 18. Initial and final (upon duplicate retesting) MIC values obtained for dalbavancin when tested against isolates selected for this study.

	Dalbavancin MIC (μg/ml)	
Collection No	Initial (surveillance)[a]	Final (this study; duplicate range)
S. aureus		
843092	0.004	0.06
835933	0.008	0.015-0.03
866944	0.008	0.015
814684	0.008	0.03
825250	0.008	0.06
813137	0.03	0.06
813140	0.03	0.06
813898	0.06	0.06
814657	0.06	0.06
816690	0.06	0.06
S. pyogenes		
830142	≤0.002	≤0.002
833085	0.004	0.008-0.015
S. agalactiae		
862038	0.004	0.015-0.03
867556	0.004	0.008-0.015
824896	0.015	0.015-0.03
825282	0.015	0.015
825754	0.015	0.015
826622	0.015	0.015
827149	0.015	0.015
S dysgalactiae		
874067	≤0.002	0.008

a. MIC results obtained and validated during the 2014 surveillance program for dalbavancin (see 14-DUR-01 report).

Reviewer comment:

In summary, variability in dalbavancin MICs were observed when dalbavancin susceptible (low end of the MIC spectrum) and dalbavancin non-susceptible isolates of *S. aureus* and streptococci were retested. Among the *S. aureus* isolates, 20.5% (8/39) showed reproducible non-susceptible MIC results (i.e. ≥0.25 μg/ml). Isolates at their respective modal MIC showed consistent results. The reasons for the variability in dalbavancin MICs upon retesting are not known. It is useful to retest non-susceptible isolates and characterize them further to better understand resistance to dalbavancin. It is not clear if isolates with an initial "non-susceptible" result to dalbavancin are retested to confirm the results at the local laboratory and how results of dalbavancin MIC retesting performed at the local laboratory are used to guide therapy. The dalbavancin non-

susceptible isolates should be submitted to a reference laboratory to assist with surveillance for resistance development and characterization of resistance mechanisms.

Other bacteria:
Please see review dated February 20, 2014 by Dr. Peter Coderre for the activity of dalbavancin against other bacteria. In summary, dalbavancin is active *in vitro* against anaerobic Gram-positive pathogens and against Gram-positive aerobic rods such as *Bacillus* spp., *Listeria* spp. and coryneforms. Like other glycopeptides, dalbavancin is generally not active against Gram-negative bacteria; however dalbavancin has *in vitro* activity against certain fastidious Gram-negative species such as *Neisseria gonorrhoeae* and *Moraxella catarrhalis.*

3.4 Interactions with other antimicrobials:

No new studies were included in this submission. In previous studies, no antagonism was observed *in vitro* when dalbavancin was combined with other antimicrobial agents that are used to treat Gram-positive and Gram-negative infections (please see review dated February 20, 2014 by Dr. Peter Coderre).

3.5 Bactericidal Activity and Time-kill Studies:

No new studies were included in this submission. The *in vitro* activity of dalbavancin is affected by the addition of serum. Dalbavancin is 93% protein bound. Studies of the bactericidal activity of dalbavancin have included determination of minimal bactericidal concentration (MBC) and time kill experiments (Report 1459B-102, Report VER001-MI-011, Lin2005a, Lin 2005b) [18, 19, 20, 21]. Dalbavancin shows time-dependent bactericidal activity *in vitro* against staphylococci and streptococci. The MBC values of dalbavancin for 20 clinical isolates of staphylococci, streptococci, and enterococci collected from the US and Europe are shown in Table 19 (Report 1459B-102)[18]. This study utilized broth microdilution CLSI methodology with (b) (4)

In time kill experiments, MRSA strain 1109400, MRSA strain 1109405 , MSSA 1109236 and MRSA 110398 exposed to dalbavancin at ≥1 μg/mL produced >3 $\log_{10}$ reduction in CFU/mL. In another study, dalbavancin at 0.12 μg/mL showed 3 $\log_{10}$ reduction in CFU/mL against 10 isolates of *S. pneumoniae* and at 1 μg/mL showed 3 $\log_{10}$ reduction in CFU/mL against 3 strains of coagulase negative *S. aureus*.

[18] 1459B-102. Bactericidal activity of dalbavancin against staphylococci, streptococci, and enterococci.
[19] VER001-MI-011. Time-kill kinetics of dalbavancin, teicoplanin, and vancomycin against *S. aureus*, *S. pyogenes*, and *E. faecalis*.
[20] Lin G, Credito K, Ednie LM, Appelbaum PC. Antistaphylococcal activity of dalbavancin, an experimental glycopeptide. Antimicrob Agents Chemother. Antimicrob Agents Chemother. 2005a ;49:770-2.
[21] Lin G, Smith K, Ednie LM, Appelbaum PC. Antipneumococcal activity of dalbavancin compared to other agents. Antimicrob Agents Chemother. 2005b;49:5182-4.

Table 19 Minimal Bactericidal Concentrations of Dalbavancin and Comparators for 20 Gram-Positive Clinical Isolates

Organism (no. tested)	Agent	MIC range (µg/mL)	MBC range (µg/mL)	MBC/MIC range
MSSA (2)	Dalbavancin	0.06	0.06-1	1-16
	Vancomycin	1	1-2	1-2
	Teicoplanin	0.5-1	0.5-4	1-4
	Gentamicin	0.25-0.5	0.25-1	1-2
	Oxacillin	0.5	2-4	4-8
MRSA (2)	Dalbavancin	0.06	0.06-0.5	1-8
	Vancomycin	1	1	1
	Teicoplanin	0.5-1	0.5-1	1
	Gentamicin	0.25-0.5	0.5-1	2
VISA, gentamicin-R (1)	Dalbavancin	1	2	2
	Vancomycin	8	8	1
	Teicoplanin	4	8	2
MRSE, gentamicin-R (3)	Dalbavancin	0.03-0.06	0.03-0.06	1
	Vancomycin	2	2	1
	Teicoplanin	2-8	4-32	2-4
S. haemolyticus, MR (2)	Dalbavancin	0.03-0.12	0.12-0.25	2-4
	Vancomycin	1-4	4->32	1->32
	Teicoplanin	0.5-32	0.5->32	1-≥2
	Gentamicin	≤0.06-4	≤0.06-4	1-≥1
S. pyogenes (3)	Dalbavancin	0.008	0.008-0.25	1-32
	Vancomycin	0.5	0.5->2	1->4
	Teicoplanin	0.03-0.06	0.03-0.5	1-8
	Levofloxacin	0.5	0.5	1
	Penicillin	≤0.03	≤0.03	≥1
Organism (no. tested)	**Agent**	**MIC range (µg/mL)**	**MBC range (µg/mL)**	**MBC/MIC range**
Viridans group streptococci (3) [a]	Dalbavancin	0.015-003	0.03-1	2-32
	Vancomycin	0.5	0.5->2	1->4
	Teicoplanin	0.03-0.12	0.06->4	1->32
	Levofloxacin	1->8	1->8	1-≥4
	Penicillin	≤0.03-8	0.12-8	1-≥4
Enterococcus spp., vancomycin-S (4) [b]	Dalbavancin	0.015-0.06	2-8	64-256
	Vancomycin	0.25-2	16->32	32->32
	Teicoplanin	≤0.12-0.25	8-16	64-≥64
	Ampicillin	0.25-0.5	8-128	256-512
	Gentamicin	8-16	8-16	1

Abbreviations: MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*; R=resistant; VISA=vancomycin-intermediate *S. aureus*; MRSE=methicillin-resistant *S. epidermidis*; MR=methicillin-resistant; S=susceptible.

[a] Include one each of *S. intermedius*, *S. mitis*, and *S. oralis*. [b] Include 2 each of *E. faecalis* and *E. faecium*.

Data from Report 1459B-102.

3.6 Pharmacokinetics:

The mean plasma C_{max} of dalbavancin administered as 1000 mg is 285 µg/mL and the minimum concentration between the first dose (1000 mg) and second dose (500 mg) is at least 20 µg/mL. The mean plasma C_{max} of dalbavancin given as 1500 mg is 411 µg/mL (Report DAL-MS-01)[22]. The levels of free drug are at least 1.4 µg/mL, as dalbavancin is 93% protein-bound in human

[22] Report DAL-MS-01. Population Pharmacokinetic Analysis of Dalbavancin Following DUR001-303 with Exploratory Exposure-Response Analysis

plasma. These concentrations are above the MIC_{90}s and the *in vitro* bactericidal concentrations of target organisms (mainly *S. aureus* and β-hemolytic streptococci). The half-life of dalbavancin is 5-7 days.

3.7 *In vivo* Activity (Animal Studies):

The efficacy of dalbavancin was evaluated in many different animal models of infections (for example, acute septicemia, thigh infection, pneumonia, granuloma pouch, and endocarditis). The efficacy against *S. aureus* (including MRSA and VISA strains), *S. epidermidis*, *S. pyogenes*, *S. pneumoniae* (including PRSP) and *B. anthracis* was evaluated in these studies (Tables 20 and 21). The studies were reviewed previously (Please see review dated February 20, 2014 by Dr. Peter Coderre). The studies showed that dalbavancin was effective in reducing bacterial load in tissues or improving survival of the animals. Only studies that evaluated the pharmacokinetic-pharmacodynamic (PK-PD) relationship are reviewed here. The neutropenic thigh model was used to model pharmacodynamics of dalbavancin in two studies (Andes and Craig 2007, Report DAL-MC-01).

Table 20. Dalbavancin: Summary of Animal Infection Model Studies with Staphylococci (Appended from the submission).

Model	Reference	Strains Utilized	Dosages	Dosage Frequency	No. of Isolates	MIC (µg/mL)	Highest MIC With Efficacy (µg/mL)a
Neutropenic mouse model	DAL-MC-001	*S. aureus* including VISA isolates	2.5-160 mg/kg IP	2 h post-infection, at intervals of 12h, 6 days	7	0.12-0.5 µg/mL	0.5 µg/mL
Immunocompetent mouse septicemia, infected IP	Candiani 1999	MSSA	Varying dosages, SC	Once, 10 min post- infection	1	0.06	0.06
Neutropenic mouse septicemia	Candiani 1999	*S. epidermidis*	Varying dosages, SC	Once, 10 min post- infection	1	0.12	0.12
Rabbit, left-sided endocarditis	Lefort 2004	MRSA and VISA	10 mg/kg IV	48 h post-infection, qd for 4 days	2	MRSA 0.5 VISA 4	4
Rabbit, left-sided endocarditis	Lefort 2004	MRSA and VISA	40 mg/kg IV	Once, 48 h post-infection	2	MRSA 0.5 VISA 4	4
Rat, left-sided endocarditis	Candiani 1999	MRSA	10 or 1.25 mg/kg IV (doubled LD)	17 h post-infection, qd for 5 days	1	0.12	0.12
Rat, left-sided endocarditis	Candiani 1999	*S. epidermidis*	2.5 or 1.25 mg/kg IV (doubled LD)	24 h post-infection, qd for 5 days	1	0.12	0.12
Rat, granuloma pouch	Jabes 2004	MSSA and MRSA	2.5, 5 or 10 mg/kg IV	Single dose 1 h post-infection (MSSA) or 3 h post-infection (MRSA)	2	MSSA ≤0.12-0.25 MRSA 0.25-5	0.25-0.5
Rabbit, subcutaneous implant	Darouiche 2004	MSSA	10 mg/kg IV	Single pre-operative dose	1	0.06	0.06
Neutropenic mouse, thigh	Report VER001-MI-013	3 MSSA and 3 MRSA	30-480 mg/kg IP	2 h post-infection, at intervals of 12, 24, 36 or 72 h, 6 days	6	0.06-0.12	0.12
Neutropenic mouse, lung	Report VER001-MI-013	MSSA	30-480 mg/kg IP	2 h post-infection, at intervals of 12, 24, 36 or 72 h, 6 days	1	0.06	0.06

[a] Some MIC values for staphylococci may be over-estimated because the requirement for P-80 was not known at the time the studies were conducted.

LD=loading dose, IP=intraperitoneal, IV=intravenous, SC=subcutaneous, qd=once daily

Table 21. Dalbavancin: Summary of Animal Infection Model Studies with Streptococci (Appended from the submission).

Model	Reference	Strains Utilized	Dosages	Dosage Frequency	No. of Isolates	MIC (µg/mL)	Highest MIC With Efficacy (µg/mL)
Immunocompetent mouse septicemia, infected IP	Malabarba 1995 Malabarba 2005	*S. pyogenes*	Varying dosages, SC	Once, 10 min post-infection	1	0.06	0.06
Immunocompetent mouse septicemia, infected IP	Candiani 1999	PSSP	Varying dosages, SC	Once, 10 min post-infection	1	0.03	0.03
Immunocompetent rat, pneumonia	Candiani 2001	PRSP	10 mg/kg IV	Once, 12 h post- infection	1	0.25	0.25
Immunocompetent and neutropenic rat, lobar pneumonia	Candiani 1999	PSSP and PRSP	1.6, 4 or 10 mg/kg IV	Single dose 12 h post-infection	2	0.015	0.015
Neutropenic mouse, thigh	Report VER001-MI-013	2 PSSP and 3 PRSP	0.6-10 mg/kg IP	2 h post-infection, at intervals of 12, 24, 36 or 72 h, 6 days	5	0.004-0.03	0.03
Neutropenic mouse, lung	Report VER001-MI-013	PSSP	0.6-10 mg/kg IP	2 h post-infection, at intervals of 12, 24, 36 or 72 h, 6 days	1	0.03	0.03

h=hour; IP=intraperitoneal, IV=intravenous, SC=subcutaneous, PSSI=penicillin-susceptible *S. pneumoniae*, PRSP=penicillin-resistant *S. pneumoniae*, na=not available.

Andes and Craig 2007 Study:

In this study, neutropenic Swiss ICR mice were used. The thighs of the mice (n = 4 for each experimental condition) were injected with 10^6 or 10^7 CFU of each of the *S. aureus* (n = 6; 3 MRSA) or *S. pneumonia* (n = 5; 3 PRSP). The dalbavancin MICs for the *S. aureus* strains ranged from 0.06 to 0.12 µg/mL, and for the *S. pneumonia* strains from 0.004 to 0.03 µg/mL. Dalbavancin was administered intraperitoneally as it results in linear PK over the dose range. The drug levels in the plasma over the dose range of 2.5 to 80 mg/kg were determined by a microbiological agar diffusion assay. Five total doses of dalbavancin ranging from 0.61 to 10 mg/kg for the *S. pneumoniae* infection and from 30 to 480 mg/kg for the *S. aureus* infection were administered over 6 days at intervals of 12, 24, 36 or 72 hours. The dose-response curve was characterized using the maximum effect model. The dose required to produce a net bacteriostatic effect over the 144-hour treatment period and the doses necessary to produce a 1- or 2-$\log_{10}$ reduction in CFU are shown in Table 22. In the *S. pneumoniae* and *S. aureus* infections, the two highest total doses were effective.

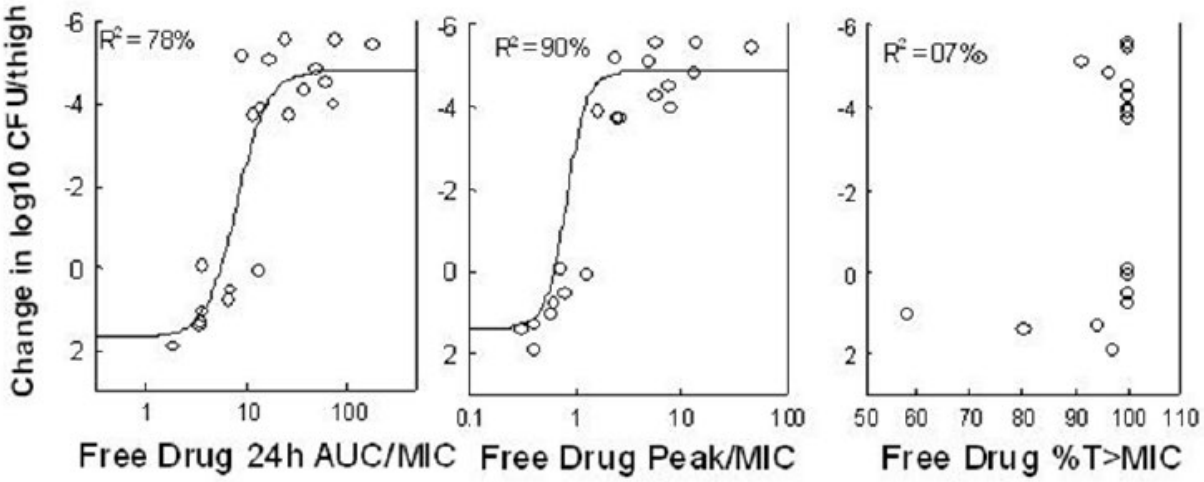
Table 22 Efficacy of Different Dosage Regimens of Dalbavancin against *S. pneumoniae* (SP) and *S. aureus* (SA) in the Neutropenic Mouse Thigh Model (Appended from submission).

Organism	MIC/ MBC (µg/mL)	2. Static Effect			3. 1-Log Kill			4. 2-Log Kill		
q24 hours regimen		mg/kg/ 24h	f24AUC/ MIC	f24AUC/ MBC	mg/kg/ 24h	f24AUC/ MIC	f24AUC/ MBC	mg/kg/ 24h	f24AUC/ MIC	f24AUC/ MBC
S. pneumoniae										
SP1199	0.004	0.40	16.0		0.49	19.4		0.57	22.7	
SP1293	0.004	0.44	17.4		0.55	21.7		0.65	25.9	
SP1325	0.008	1.46	29.0		1.6	31.8		1.73	34.5	
SP1329	0.008	0.90	18.0		1.18	23.5		1.45	26.7	
SP10813	0.03	1.34	7.5		1.54	8.7		1.75	9.9	
Mean ±SD		**0.91 ±0.44**	**17.6 ± 6.9**		**1.1 ±.0.47**	**21 ± 7.4**		**1.23 ±0.52**	**24.3 ± 8.2**	
S. aureus										
SA25923	0.12/0.25	42.7	216	52	51.2	250	60	60	289	69.3
SA33591	0.12/0.25	22.3	96.2	46	27.7	121	58.3	33.5	157	74.3
SA31005	0.06/0.12	49.3	483	242	-	-	-	-	-	-
MRSA	0.06/0.25	37.7	374	93	45.3	452	109	53.5	519	125
SA Smith	0.12/0.25	33.5	156	75	50.7	248	119	73.5	361	173
Mean ±SD		**37.1 ±9.1**	**265 ± 143**	**101 ± 72**	**43.7 ±9.5**	**268 ± 119**	**86.6 ± 27.6**	**55 ±14**	**332 ± 131**	**110 ± 42**
q 72 hours regimen		**mg/kg/ 72h**								
S. pneumoniae										
SP1325	0.008	0.83	6.0		0.99	8.8		1.16	17.6	
SP1293	0.004	1.01	14.1		1.28	18		1.68	23.8	
SP1199	0.004	0.72	10.3		0.85	12.1		0.99	35.3	
SP1396	0.008	0.52	4.0		0.61	4.3		0.69	4.8	
SP10813	0.03	0.71	1.4		0.77	1.6		0.82	1.6	
Mean±SD		**0.77±0.18**	**7.2 ±4.5**		**0.93±0.24**	**9.0 ± 5.8**		**1.13±0.36**	**16.6 ±12.3**	
S. aureus										
SA25923	0.12/0.50	160	274	66	185	317	76.1	214	367	88.1
SA33591	0.12/0.25	74	123	59	93	160	76.6	114	195	94
MRSA	0.06/0.25	43	147	35.3	62	202	48.8	85	292	70
SA Smith	0.12/0.25	59	96	46.1	95	163	78.0	148	254	22
SA307109	0.06/0.50	31	94	11.3	34	108	12.9	37	121	14.6
SA31005	0.06/0.12	67.7	223	112	94.6	325	163	127	364	217
Mean ±SD		**72 ±41**	**160 ± 67**	**55 ± 31**	**94 ±46**	**213 ± 81.4**	**75.9 ± 45.2**	**120 ±54**	**266 ± 88**	**101 ± 61**

Data from Report VER001-MI-013.

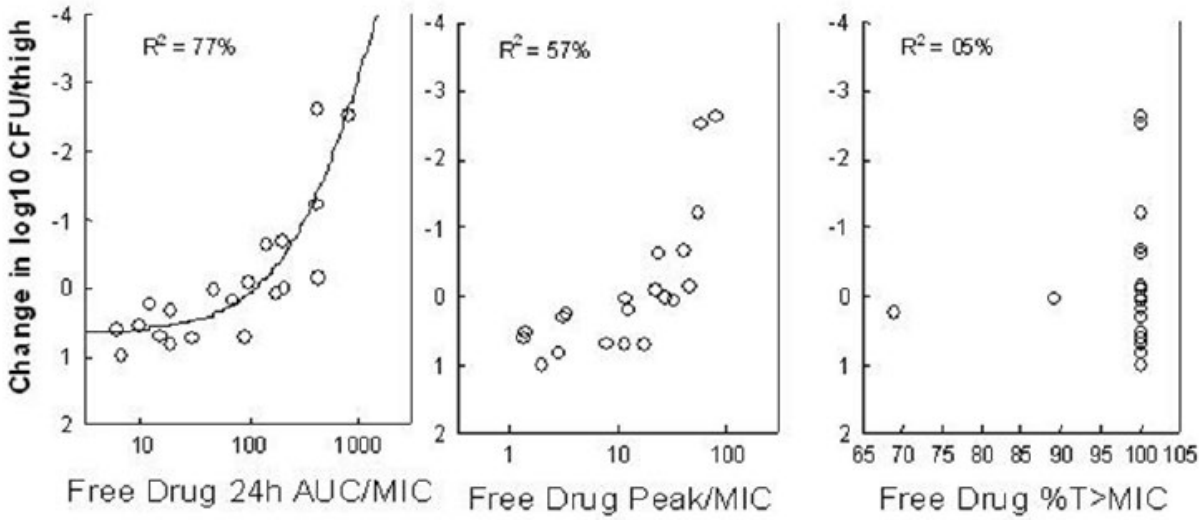
The PK/PD parameter that best correlated with efficacy was determined by plotting the CFU/thigh at the end of 144 hours of therapy to the 24-hour free AUC/MIC ratio, the free peak/MIC ratio, and the percentage of the dosing interval over which free serum levels exceeded the MIC(%T>MIC). For both *S. pneumoniae* (Figure 2) and *S. aureus* (Figure 3), the 24-hour AUC/MIC ratio correlated with efficacy and the correlation between time above MIC and efficacy was not evident possibly due to limited data.

Figure 2. Relationship between PK/PD Parameters and Efficacy of Dalbavancin against *S. pneumoniae.*



Data from Report VER001-MI-013

Figure 3. Relationship between PK/PD Parameters and Efficacy of Dalbavancin against *S. aureus*



Data from Report VER001-MI-013

Andes 2015 (Report DAL-MC-01):

In this new study, the same mouse model was used as in the 2007 study above except that the MIC values of the strains were determined using the current CLSI method and a more robust LC-MS assay was used to measure drug levels in plasma. Approximately 10^7 CFU of each *S. aureus* isolate (n = 7; 4 VISA) was injected into the thighs of the mice (n = 4 for each experimental condition). The dalbavancin MIC values for the *S. aureus* isolates ranged from 0.12 µg/mL to0.5 µg/mL (6 isolates had dalbavancin MIC >0.12 µg/mL; Table 23). Seven dose levels of dalbavancin ranging from 2.5 to 160 mg/kg were administered intraperitoneally every 12 hours over a period of 144 hours or 6 days. As in the previous study, the exposure response was described by AUC/MIC ($R^2 = 0.86$).

Table 23. Study Strains and Dalbavancin *in vitro* susceptibility (Appended from the submission).

Prior Study		Current Study		
Isolate	MIC (mg/L)	Isolate	MIC (mg/L)	Comment
25923	0.12	LSI653	0.25	(VAN=2)
33591	0.12	LSI1848	0.12	
31005	0.06	LSI1854	0.5	
MRSA	0.06	LSI1856	0.25	VISA (VAN=4)
Smith	0.06	LSI1857	0.25	VISA (VAN=4)
307106	0.06	LSI1861	0.25	VISA (VAN=4)
		LSI1862	0.5	VISA (VAN=4)

The mean total dose and the free drug AUC/MIC for bacteriostasis, 1-log kill and 2-log kill for all isolates is shown in Table 24. The AUC/MIC values in this study were 3 to 9.8 times less than the previous study possibly due to the study design and drug assay (Tables 25 and 26).

Table 24. Efficacy of of Dalbavancin against *S. aureus* in the Neutropenic Mouse Thigh Model

Organism		Static Effect		1-Log Kill		2-Log Kill	
q12 hours regimen	DAL/VAN MIC[1] (µg/mL)	Dose mg/kg/24h	f24-hAUC/ MIC	Dose mg/kg/24h	f24-hAUC/ MIC	Dose mg/kg/24 h	f24-hAUC/ MIC
LSI653	0.25/2	14.93	27.77	27.20	49.52	54.09	93.07
LSI1848	0.12/2	15.17	56.49	31.45	112.81	62.75	214.21
LSI1854	0.5/2	15.00	13.95	35.80	31.73	--	--
LSI1856	0.25/4	15.21	28.32	30.88	55.49	60.05	102.73
LSI1857	0.25/4	14.34	26.59	26.72	48.74	60.05	102.72
LSI1861	0.25/4	13.55	25.00	24.63	45.35	44.38	77.35
LSI1862	0.5/4	12.64	11.60	32.92	29.39	85.46	76.66
Mean	--	**14.41**	**27.10**	**29.94**	**53.29**	**61.13**	**111.12**
Median	---	**14.93**	**26.59**	**30.88**	**48.74**	**60.05**	**97.90**
SD	--	**0.98**	**14.62**	**3.93**	**27.93**	**13.62**	**51.81**

[1] MIC testing conducted at (b) (4) DAL=dalbavancin VAN=vancomycin

Source: Report DAL-MC-01

Table 25. Dalbavancin plasma pharmacokinetic parameters in mice from the present and prior study.

Dose (mg/kg)	Prior Study			Current Study		
	Cmax (µg/ml)	AUC (mg*h/L)	$T_{1/2}$ (h)	Cmax (µg/ml)	AUC (mg*h/L)	$T_{1/2}$ (h)
2.5	7.4	98	13.1	8.82	65.6	4.1
10	34.8	579	12.5	32.2	271	6.3
40	385	5360	10.4	82.3	948	6.5
80	663	10600	9.7	247	2784	6.8
160				413	6956	9.3

Table 26. Comparison of 2007 and 2015 Neutropenic Mouse Model Studies: Mouse Plasma Pharmacokinetic Data.

Andes 2007			Andes 2015		
S. aureus	Static Effect	1-Log Kill	*S. aureus*	Static Effect	1-Log Kill
q24 hour regimen	f24AUC/MIC	f24AUC/MIC	q12 hours regimen	f24AUC/MIC	f24AUC\MIC
Mean	**265**	**268**	Mean	**27.10**	**53.29**
Median	216	249	Median	26.59	48.74
SD	143	119	SD	14.62	27.93

Source: Andes and Craig 2007; Report DAL-MC-01

Reviewer comment:
The targets of free drug AUC/MIC to achieve stasis and 1log kill in the new study were 27 and 49 hours, respectively. These AUC/MIC values were lower the previous study possibly due to study design and drug assay.

4 CLINICAL STUDIES:

This efficacy supplement includes results of a phase 3b, double-blind, multicenter, randomized trial (DUR001-303) that evaluated the safety and efficacy of single 1500 mg IV dalbavancin dose to two dose IV dalbavancin regimen (1000 mg on Day 1 followed by 500 mg on Day 8) for the treatment of ABSSSI.

DUR001-303:
In this Phase 3b study, a total of 698 adult patients, ages 18 to 85, with ABSSI were randomized (1:1 ratio) to the two treatment groups. Patients with an ABSSSI (major cutaneous abscess, surgical site or traumatic wound infection, or cellulitis) suspected or confirmed to be caused by Gram-positive bacteria accompanied by erythema and at least 2 additional local signs of ABSSSI (purulent drainage/discharge, fluctuance, heat/localized warmth, tenderness to palpation, and swelling/induration), and at least 1 systemic sign of infection (fever with body temperature ≥38°C within 24 hours of baseline; white blood cell count >12,000 cells/mm^3; or ≥10% band forms irrespective of peripheral WBC count) were included in the study. Patients were excluded if they participated in another investigational drug study within 30 days prior to study enrollment, received systemic antibiotic with Gram-positive spectrum except those who received a single dose of antibacterial (half-life ≤ 12 hours) prior to randomization, had infection due to

known organism resistant to dalbavancin or vancomycin (vancomycin MIC>8 μg/mL), or where the infection was caused solely by Gram negative bacteria. Additionally, immunosuppressed and transplant patients, those with evidence of meningitis, necrotizing fasciitis, gangrene, septic arthritis, osteomyelitis; endovascular infection or those requiring surgical intervention were excluded.

Efficacy assessments included clinical assessments (evidence of systemic inflammation and infection site assessment) and microbiology (blood cultures and infection site specimen collection for identification and susceptibility testing). Efficacy assessments were performed on Day 3-4; on Day 8, when patients were administered the second dose of study drug; on Day 14-15, the End of Treatment (EOT) Visit; and on Day 28, the Final Visit. The primary outcome measure was clinical response, defined as a reduction of at least 20% in lesion size at 48 to 72 hours in the intent-to-treat (ITT) population (classified as clinical responders and non-responders in the dataset). For the secondary efficacy analyses, the percentages of patients in each treatment group who demonstrated clinical success at EOT (Day 14-15 ± 2 days) or the Final Visit (Day 28 ±2 days) after the initiation of study drug were compared in the ITT, and clinically evaluable (CE) populations.

Clinical success at EOT and Final Visits were defined as follows:
• A patient's lesion area had decreased by ≥80% from baseline at EOT and by ≥90% from baseline at the Final Visit.
• The patient's temperature was ≤37.6°C;
• Local signs of tenderness to palpation and swelling/induration were mild;
• For patients with a wound infection, the severity of purulent drainage was improved and mild compared to baseline;
• Local signs of fluctuance and localized heat/warmth were improved from baseline and mild at the EOT visit and absent at the Final Visit.

If patients did not meet the clinical success criteria, they were classified as a clinical failure. A patient was defined as having indeterminate clinical status, if any of the data needed to determine clinical success or clinical failure, as defined above, were missing. Microbiological outcome was not assessed in this study.

Microbiology Laboratory Procedures:
The specimens collected for the various infection types are shown in in Table 27. Blood cultures were drawn at baseline (prior to study drug treatment) from 2 different anatomical sites and not through an existing intravascular line for 2 sets of cultures (each set was to be cultured using both aerobic and anaerobic methods). If positive, blood cultures were to be repeated 48 to 72 hours after the first dose of study drug until negative.

Gram staining was performed on each specimen obtained from the infected site. Culture and susceptibility to vancomycin and dalbavancin was performed at the local laboratory. Isolates were also sent to the central laboratory (b) (4) (b) (4) for confirmation of identification and *in vitro* susceptibility testing. When the central laboratory was unable to recover the isolate, data from local laboratory

were included in the dataset and used for analysis. The study used a provisional breakpoint for susceptibility of dalbavancin to Gram-positive organisms, including methicillin sensitive and methicillin resistant *S. aureus*, of <0.25 µg/mL. Disc diffusion interpretive criteria were not available for dalbavancin.

The following organisms were considered as a pathogen when isolated from an acceptable ABSSSI specimen:
- *Staphylococcus aureus*
- Group A (*Streptococcus pyogenes*)
- Group B (*Streptococcus agalactiae*)
- Group C β-hemolytic streptococci
- *Streptococcus anginosus-milleri* Group (e.g., *Streptococcus anginosus, Streptococcus intermedius, Streptococcus constellatus*)
- *Enterococcus faecalis*
- *Enterococcus faecium*
- Gram-positive anaerobes

Table 27: Infection Specimen Collection Method.

Subtype of Infection	Source of Material	Method of Collection*
Cellulitis	• Aspirate • Punch biopsy	• After cleansing the skin at the leading edge of erythema, non-bacteriostatic sterile saline is injected and aspirated or a punch biopsy can be performed, as medically appropriate
Abscess	• Purulent fluid • Biopsy material	• Aseptic aspiration of purulent material/fluid (aspiration alone does not define the lesion as an abscess). • Biopsy material obtained from I&D under sterile conditions; only appropriate for the initial I&D or for worsening of the infection requiring discontinuation of study drug
Traumatic wound	• Scrapings from wound base • Biopsy material from wound base	• After cleansing (with non-bacteriostatic saline) and debriding the wound bed, and using sterile techniques, scrape ulcer/wound base with sterile dermal curette or scalpel to obtain tissue • After following above procedure, biopsy tissue at the base of the lesion • Any procedure performed after baseline should only be performed for worsening of the infection requiring discontinuation of study drug
Surgical site infection	• Scrapings from base of wound • Biopsy material from base of surgical site	• After cleansing (with non-bacteriostatic saline) and debriding the surgical site, and using sterile techniques, scrape the base of the lesion with sterile dermal curette or scalpel to obtain tissue • After following above procedure, biopsy tissue at the base of the lesion • Any procedure performed after baseline should only be performed for worsening of the infection requiring discontinuation of study drug

* Prior to collection of abSSSI site specimen(s), the abSSSI site is to be prepared by a standard of care surgical site skin preparation method with the appropriate application of an antiseptic agent such as: an

(b) (4)

Reviewer comment:
(b) (4) belongs to the Viridans Group Streptococci and are normal inhabitants of oral cavity. These organisms are considered as contaminants unless associated with endocarditis.

The various study populations are described below:

MODIFIED INTENT-TO-TREAT/SAFETY POPULATION (mITT)
All patients in the ITT population who received at least 1 (active) dose of dalbavancin are included in the mITT population.

CLINICALLY EVALUABLE POPULATIONS (CE)
These included all patients from the mITT populations who were clinically evaluable at EOT or Final Visit. Two different CE populations are defined based on the timing of the outcome assessment to be evaluated: CE-EOT and CE-Final Visit.

MICROBIOLOGICAL INTENT-TO-TREAT POPULATION (microITT)
The microITT population includes all patients in the ITT population who had at least one Gram-positive pathogen isolated at baseline, from either a blood culture or culture of sample obtained from the ABSSSI lesion.

MICROBIOLOGICAL MODIFIED INTENT-TO-TREAT POPULATION (micro-mITT)
The micro-mITT population includes all patients in the mITT population who also met criteria to be included in the microITT population.

MICROBIOLOGICALLY EVALUABLE POPULATIONS (ME)
Each ME population included only patients who qualified to be included in the microITT population and the respective CE population.

Study Results:
The number of patients in each analysis population is provided in the Table 28.

Table 28: Analysis populations for study DUR001-303.

Analysis Population	Dalbavancin Single Dose N=349 n (%)	Dalbavancin Two Doses N=349 n (%)	Total N=698 n (%)
ITT Population	349/349 (100.0)	349/349 (100.0)	698/698 (100.0)
mITT Population	349/349 (100.0)	346/349 (99.1)	695/698 (99.6)
Safety Population	349/349 (100.0)	346/349 (99.1)	695/698 (99.6)
CE-EOT Population	302/349 (86.5)	302/349 (86.5)	604/698 (86.5)
CE-FV Population	271/349 (77.7)	267/349 (76.5)	538/698 (77.1)
MicroITT Population	210/349 (60.2)	220/349 (63.0)	430/698 (61.6)
Micro-mITT Population	210/349 (60.2)	220/349 (63.0)	430/698 (61.6)
ME-EOT Population	176/349 (50.4)	186/349 (53.3)	362/698 (51.9)
ME-FV Population	156/349 (44.7)	163/349 (46.7)	319/698 (45.7)

Abbreviations: ITT = Intent-to-treat; mITT = Modified Intent-to-treat; CE = Clinically Evaluable; ME = Microbiologically Evaluable; MicroITT = Microbiological Intent-to-Treat; Micro-mITT = Microbiological modified Intent=to=treat; FV = Final Visit; EOT = End of treatment; N = Number of patients in the ITT population;

For the microbiology analyses described below, the microITT, ME-EOT, and ME-Final Visit populations were analyzed using datasets AXPATH and FDARQST1.

The microITT population consisted of 430 patients total; 220 patients received two doses of dalbavancin IV (1000 mg on day 1 followed by 500 mg on day 8) and 210 patients received a single dose of dalbavancin IV (1500 mg). The infection types in the two groups are shown below:

Infection Type	**Dalbavancin IV (1000mg + 500 mg) (n = 220)**	**Dalbavancin IV (1500 mg) (n = 210)**
Cellulitis	83	66
Major Abscess	71	69
Traumatic Wound/ Surgical site Infection	66	75

The specimen types in the two groups were as follows:

Specimen Type*	**Dalbavancin IV (1000mg + 500 mg) (Number of specimens = 228)**	**Dalbavancin IV (1500 mg) (Number of specimens = 218)**
ABSSSI	218	206
Blood	10	12

***Patients could have an ABSSSI and blood specimen pathogen identified.

A majority of patients in both treatment groups had monomicrobial infections (Table 29). Approximately, a quarter of patients (n = 58) had polymicrobial infections in each of the two dalbavancin arms.

Table 29: Monomicrobial and Polymicrobial Infections at Baseline (MicroITT Population)

	Dalbavancin Treatment Group, n (%) [a]	
	Single-Dose (N = 210)	**Two-Dose (N = 220)**
Monomicrobial infection	152 (72.4)	162 (73.6)
Polymicrobial infection	58 (27.6)	58 (26.4)
Polymicrobial Gram-positive infection	39 (18.6)	32 (14.5)
Polymicrobial mixed Gram-positive and Gram-negative infection	16 (7.6)	26 (11.8)

[a] Percentages are calculated based on n/N. If there was more than 1 pathogen was identified at baseline, the infection was considered polymicrobial, including infections with both MRSA and MSSA. Pathogens were identified as reported by the central laboratory except in cases where no central laboratory identification was available; in these cases, the local laboratory identification was used.

A total of 402 patients (DALB 1000 mg + 500 mg = 206; DALB 1500 mg = 196) had infection due to gram positive aerobic pathogen at baseline. The gram positive aerobic baseline pathogens in the two groups are shown in Table 30. The majority of the infections in the patients were due to *S. aureus* followed by *S. pyogenes* and *S. intermedius*.

Table 30: Baseline gram positive aerobic pathogen in the two treatment arms in the microITT and ME populations in study DUR001-303.

Organism	Treatment Group		
	Dalbavancin One-dose N=210 (%)[a]	Dalbavancin 2-dose N=220 (%)[a]	Total N =430(%)[b]
MicroITT Population			
Number of Patients with at least one Gram-positive aerobic pathogen	196 (93.3)	206 (93.6)	402 (93.5)
Staphylococcus aureus	139 (66.2)	156 (70.9)	295 (68.6)
MSSA	103 (49.0)	96 (43.6)	199 (46.3)
MRSA	36 (17.1)	61 (27.7)	97 (22.6)
Staphylococcus haemolyticus	2 (1.0)	1 (0.5)	3 (0.7)
Staphylococcus warneri	1 (0.5)	0	1 (0.2)
Streptococcus pyogenes	14 (6.7)	22 (10.0)	36 (8.4)
Streptococcus agalactiae	6 (2.9)	6 (2.7)	12 (2.8)
Streptococcus Group C	1 (0.5)	1 (0.5)	2 (0.5)
Streptococcus Group F	1 (0.5)	1 (0.5)	2 (0.5)
Streptococcus Group G	0	1 (0.5)	1 (0.2)
Streptococcus anginosus group	0	1 (0.5)	1 (0.2)
Streptococcus anginosus	6 (2.9)	2 (0.9)	8 (1.9)
Streptococcus constellatus	11 (5.2)	6 (2.7)	17 (4.0)
Streptococcus intermedius	16 (7.6)	11 (5.0)	27 (6.3)
Streptococcus gallolyticus	0	1 (0.5)	1 (0.2)
Streptococcus dysgalactiae	4 (1.9)	3 (1.4)	7 (1.6)
[redacted]			(b) (4)
Streptococcus sanguinis	3 (1.4)	2 (0.9)	5 (1.2)
Viridans group streptococci	0	2 (0.9)	2 (0.5)
Enterococcus faecalis	4 (1.9)	10 (4.5)	14 (3.3)
Enterococcus faecium	2 (1.0)	1 (0.5)	3 (0.7)
Eggerthella lenta	0	1 (0.5)	1 (0.2)
Dermabacter hominis	1 (0.5)	0	1 (0.2)
Gemella morbillorum	0	1 (0.5)	1 (0.2)
Clostridium perfringens	4 (1.9)	2 (0.9)	6 (1.4)
Clostridium senegalese	1 (0.5)	0	1 (0.2)
Clostridium tertium	0	1 (0.5)	1 (0.2)
Peptostreptococcus asaccharolyticus	1 (0.5)	0	1 (0.2)
Peptostreptococcus anaerobius	1 (0.5)	0	1 (0.2)
Peptostreptococcus magnus	1 (0.5)	0	1 (0.2)
Peptostreptococcus micros	1 (0.5)	0	1 (0.2)
Peptostreptococcus spp	0	1 (0.5)	1 (0.2)
Propronibacterium acnes	2 (1.0)	0	2 (0.5)
Finegoldia magna	0	2 (0.9)	2 (0.5)
Peptoniphilus asaccharolyticus	0	4 (1.8)	4 (0.9)

Table 30: Baseline gram positive aerobic pathogen in the two treatment arms in the microITT and ME populations in study DUR001-303. Continued.

Organism	Treatment Group		
	Dalbavancin One-dose N=210 (%)[a]	Dalbavancin 2-dose N=220 (%)[a]	Total N =430(%)[b]
MEEOT	N=176 (%)	N=186 (%)	N=362 (%)
Total baseline isolates	172 (97.7)	179 (96.2)	351 (97.0)
Streptococcus aureus	123 (69.9)	137 (73.7)	260 (71.8)
MSSA	91 (51.7)	86 (46.2)	177 (48.9)
MRSA	32 (18.2)	52 (28.0)	84 (23.2)
Staphylococcus haemolyticus	2 (1.1)	1 (0.5)	3 (0.8)
Staphylococcus warneri	1 (0.6)	0	1 (0.3)
Streptococcus pyogenes	13 (7.4)	18 (9.7)	31 (8.6)
Streptococcus agalactiae	3 (1.7)	3 (1.6)	6 (1.7)
Streptococcus Group C	1 (0.6)	1 (0.5)	2 (0.6)
Streptococcus Group F	1 (0.6)	0	1 (0.3)
Streptococcus Group G	0	1 (0.5)	1 (0.3)
Streptococcus anginosus group	0	1 (0.5)	1 (0.3)
Streptococcus anginosus	5 (2.8)	1 (0.5)	6 (1.7)
Streptococcus constellatus	8 (4.5)	5 (2.7)	13 (3.6)
Streptococcus intermedius	16 (9.1)	9 (4.8)	25 (6.9)
Streptococcus gallolyticus	0	1 (0.5)	1 (0.3)
Streptococcus dysgalactiae	3 (1.7)	3 (1.6)	6 (1.7)
			(b) (4)
Streptococcus sanguinis	3 (1.7)	2 (1.1)	5 (1.4)
Viridans group streptococci	0	2 (1.1)	2 (0.6)
Enterococcus faecalis	3 (1.7)	7 (3.8)	10 (2.8)
Enterococcus faecium	1 (0.6)	1 (0.5)	2 (0.6)
Dermabacter hominis	1 (0.6)	0	1 (0.3)
Eggerthella lenta	0	1 (0.5)	1 (0.3)
Gemella morbillorum	0	1 (0.5)	1 (0.3)
Clostridium perfringens	2 (1.1)	2 (1.1)	4 (1.1)
Clostridium senegalese	1 (0.6)	0	1 (0.3)
Clostridium tertium	0	1 (0.5)	1 (0.3)
Peptostreptococcus asaccharolyticus	1 (0.6)	0	1 (0.3)
Peptostreptococcus magnus	1 (0.6)	0	1 (0.3)
Peptostreptococcus micros	1 (0.6)	0	1 (0.3)
Peptostreptococcus spp	0	1 (0.5)	1 (0.3)
Propronibacterium acnes	1 (0.6)	0	1 (0.3)
Finegoldia magna	0	2 (1.1)	2 (0.6)
Peptoniphilus asaccharolyticus	0	2 (1.1)	2 (0.6)

[a] The percentages are calculated as 100 x (n/N). The same pathogen identified from both the blood and the culture of the ABSSSI site is counted only once in the summary. If the same pathogen is isolated more than once from the same site (ABSSSI or blood), it is counted only once in the summary. Baseline pathogens include isolates from mixed infection.

The number and percentage of clinical responders at 48-72 hours stratified by baseline Gram-positive pathogens in the microITT population are shown in Table 31. The number and percentage of patients with clinical success at EOT and final visit by baseline Gram-positive pathogen in the microITT and ME populations are shown in Tables 32 and 33. The number and percentage of patients with clinical success at EOT and final visit by baseline Gram-positive pathogen in the microITT and ME populations with single infections are shown in Table 34. The majority of the patients had methicillin-sensitive *S. aureus* as the baseline pathogen followed by methicillin-resistant *S. aureus*, *Streptococcus anginosus* group, and *Streptococcus pyogenes*. The clinical responders with baseline MSSA at 48-72 hours were similar in the two dalbavancin arms (89.3% in single dose arm and 89.6% in two dose arm). The single dose dalbavancin had a slightly better response in patients with baseline MRSA compared to two doses of dalbavancin (86% versus 78.7%). The response rates for *Streptococcus anginosus* group were 93.9% in the dalbavancin single dose group and 100% in the group receiving two doses. In the case of *S. pyogenes*, all 14 patients showed clinical response in the dalbavancin single dose group compared to 81.8% (18/22) in the group receiving two doses. Similar clinical success rates were observed at EOT and follow up in patients with baseline *S. aureus, Streptococcus anginosus* group, *S. pyogenes* receiving single dose or two doses of dalbavancin (Tables 32 and 33).

The number of patients with *Enterococcus* species in this study was small (6 patients in the single dose group compared to 11 in the two-dose group). The clinical responders with baseline *E. faecalis* at 48-72 hours were 100% (4/4) in single dose arm and 80% (8/10) in two doses arm. Only one of the two patients with *E. faecium* in the dalbavancin single dose group was a clinical responder at 48-72 hours. One patient with *E. faecium* receiving two doses of dalbavancin also was a clinical responder at 48-72 hours. Similar clinical success rates were observed at EOT and follow-up visit in these patients (Table 36).

Few patients had (b) (4) identified as baseline pathogens in the two treatment arms (Table 31). The response rate for (b) (4) in the dalbavancin single dose compared to 100% (5/5) in patients receiving two doses of dalbavancin. However, please note that (b) (4) is not considered as a pathogen for this indication. Few patients had *S. dysgalactiae* as the baseline pathogens in the two treatment arms (see Table 31; n = 4 in single dose arm and n = 3 in the two doses arm). All patients responded clinically to treatment at 48-72 hours.

Table 31 Clinical Responders at 48-72 hours by baseline Gram-positive pathogen (MicroITT population).

Baseline Pathogen*	**Dalbavancin (1500 mg) n/N (%)**	**Dalbavancin (1000 mg + 500 mg) n/N (%)**
Staphylococcus aureus	123/139 (88.5)	133/157 (84.7)
MRSA	31/36 (86.1)	48/61 (78.7)
MSSA	92/103 (89.3)	86/96 (89.6)
Staphylococcus haemolyticus	2/2 (100.0)	1/1(100.0)
Staphylococcus warneri	1/1 (100.0)	0/0
Streptococcus agalactiae	6/6 (100.0)	4/6 (66.7)
Streptococcus anginosus group	31/33 (93.9)	19/19 (100.0)
Streptococcus anginosus	6/6 (100.0)	2/2 (100.0)
Streptococcus constellatus	10/11 (90.9)	6/6 (100.0)
Streptococcus intermedius	15/16 (93.8)	11/11 (100.0)
Streptococcus dysgalactiae	4/4 (100.0)	3/3 (100.0)
Streptococcus pyogenes	14/14 (100.0)	18/22 (81.8)
Enterococcus faecalis	4/4 (100.0)	8/10 (80.0)
Enterococcus faecium	1/2 (50.0)	1/1(100.0)
Dermabacter hominis	1/1 (100.0)	0/0
Gemella morbillorum	0/0	1/1 (100.0)
Group C β-hemolytic streptococci	1/1 (100.0)	0/1 (0.0)
Group F streptococci	1/1 (100.0)	1/1 (100.0)
Group G streptococci	0/0	1/1 (100.0)
		(b) (4)
Streptococcus sanguinis	2/3 (67.0)	2/2(100.0)
Streptococcus viridans group	0/0	2/2 (100.0)

*Includes mixed pathogens
n = Number of patients with the respective observation;
N = Number of MicroITT patients with the respective pathogen at baseline; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus.*

Table 32: Clinical Success at EOT and final visit by baseline Gram-positive pathogen (MicroITT populations).

Baseline Pathogen*	**Dalbavancin Treatment Group, n/N (%)**			
	EOT Visit		**Final Visit**	
	Single-dose	**Two-dose**	**Single-dose**	**Two-dose**
MicroITT population				
Staphylococcus aureus	122/139 (87.8)	144/157 (91.7)	124/139 (89.2)	141/157 (89.8)
MRSA	30/36 (83.3)	53/61 (86.9)	31/36 (86.1)	55/61 (90.2)
MSSA	92/103 (89.3)	91/96 (94.8)	93/103 (90.3)	86/96 (89.6)
Staphylococcus haemolyticus	2/2 (100.0)	1/1(100.0)	2/2 (100.0)	1/1(100.0)
Staphylococcus warneri	1/1 (100.0)	0/0	1/1 (100.0)	0/0
Streptococcus agalactiae	5/6 (83.3)	5/6 (83.3)	5/6 (83.3)	5/6 (83.3)
Streptococcus anginosus group	27/33 (81.8)	17/19 (89.5)	29/33 (87.9)	17/19 (89.5)
Streptococcus anginosus	5/6 (83.3)	2/2 (100.0)	6/6 (100.0)	2/2 (100.0)
Streptococcus constellatus	9/11 (81.3)	6/6 (100.0)	10/11 (90.9)	6/6 (100.0)
Streptococcus intermedius	13/16 (81.3)	9/11 (81.8)	13/16 (81.3)	9/11 (81.8)
Streptococcus dysgalactiae	4/4 (100.0)	3/3 (100.0)	4/4 (100.0)	3/3 (100.0)
Streptococcus pyogenes	13/14 (92.9)	18/22 (81.8)	13/14 (92.9)	19/22 (86.4)
Enterococcus faecalis	4/4 (100.0)	10/10 (100.0)	4/4 (100.0)	9/10 (90.0)
Enterococcus faecium	1/2 (50.0)	1/1(100.0)	1/2 (50.0)	1/1(100.0)
Dermabacter hominis	1/1 (100.0)	0/0	1/1 (100.0)	0/0
Gemella morbillorum	0/0	1/1 (100.0)	0/0	1/1 (100.0)
Group C β-hemolytic streptococci	1/1 (100.0)	0/1 (0.0)	1/1 (100.0)	0/1 (0.0)
Group F streptococci	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Group G streptococci	0/0	1/1 (100.0)	0/0	1/1 (100.0)
[redacted]				(b) (4)
Streptococcus sanguinis	2/3 (67.0)	1/2(50.0)	2/3 (67.0)	1/2(50.0)
Streptococcus viridans group	0/0	2/2 (100.0)	0/0	2/2 (100.0)

*Includes mixed infections
MicroITT = Microbiological intent-to-treat; n = Number of patients with the respective observation;
N = Number of MicroITT patients with the respective pathogen at baseline;
MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Table 33: Clinical Success at EOT and final visit by baseline Gram-positive pathogen (ME populations).

Baseline Pathogen*	**Dalbavancin Treatment Group, n/N (%)**			
	EOT Visit		**Final Visit**	
	Single-dose	**Two-dose**	**Single-dose**	**Two-dose**
ME population				
Staphylococcus aureus	112/123 (91.1)	132/138 (95.6)	105/110 (95.5)	119/123 (96.7)
MRSA	29/32 (90.6)	48/52 (92.3)	29/31 (93.5)	45/48 (93.8)
MSSA	83/91 (91.2)	84/86 (97.7)	76/79 (96.2)	74/75 (98.6)
Staphylococcus haemolyticus	2/2 (100.0)	1/1(100.0)	2/2 (100.0)	0/1(0.0)
Staphylococcus warneri	1/1 (100.0)	0/0	1/1 (100.0)	0/0
Streptococcus agalactiae	3/3 (100.0)	2/3 (66.7)	2/2 (100.0)	2/3 (66.7)
Streptococcus anginosus group	24/29 (82.8)	15/15 (100.0)	24/26 (92.3)	11/11 (100.0)
Streptococcus anginosus	4/5 (80.0)	1/1 (100.0)	4/4 (100.0)	0/0
Streptococcus constellatus	7/8 (87.5)	5/5 (100.0)	8/8 (100.0)	3/3 (100.0)
Streptococcus intermedius	13/16 (81.3)	9/9 (100.0)	12/14 (85.7)	8/8 (100.0)
Streptococcus dysgalactiae	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)
Streptococcus pyogenes	12/13 (92.3)	16/18 (88.9)	10/10 (100.0)	17/18 (94.4)
Enterococcus faecalis	3/3 (100.0)	7/7 (100.0)	3/3 (100)	6/7 (85.7)
Enterococcus faecium	1/1 (50.0)	0/1(0)	1/1 (50.0)	0/1(0)
Dermabacter hominis	0/0	1/1 (100.0)	0/0	1/1 (100.0)
Gemella morbillorum	0/0	1/1 (100.0)	0/0	1/1 (100.0)
Group C β-hemolytic streptococci	1/1 (100.0)	0/1 (0.0)	1/1 (100.0)	0/1 (0.0)
Group F streptococci	1/1 (100.0)	0/0	1/1 (100.0)	0/0
Group G streptococci	0/0	1/1 (100.0)	0/0	1/1 (100.0)
[redacted]				(b) (4)
Streptococcus sanguinis	2/3 (66.7)	1/2 (50%)	2/3 (66.7)	2/2 (100.0)
Streptococcus viridans group	0/0	2/2 (100.0)	0/0	2/2 (100.0)

*Includes mixed infections
ME = Microbiologically evaluable at the respective clinic visit; n = Number of patients with the respective observation; N = Number of ME patients with the respective pathogen at baseline;
MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Table 34: Clinical Success at EOT and final visit by baseline Gram-positive pathogen (MicroITT and ME populations with monoinfections).

Baseline Pathogen*	**Dalbavancin Treatment Group, n/N (%)**			
	EOT Visit		**Final Visit**	
	Single-dose	**Two-dose**	**Single-dose**	**Two-dose**
MicroITT population				
Staphylococcus aureus	88/102 (86.3)	101/110 (91.8)	89/102 (87.3)	100/110 (90.9)
MRSA	27/32 (84.4)	41/46 (89.1)	28/32 (87.5)	42/46 (91.3)
MSSA	61/70 (87.1)	60/64 (93.8)	61/70 (87.1)	58/64 (90.6)
Streptococcus agalactiae	2/2 (100.0)	1/2 (50.0)	2/2 (100.0)	1/2 (50.0)
Streptococcus anginosus group	14/17 (82.4)	9/10 (90.0)	14/17 (82.4)	9/10 (90.0)
Streptococcus anginosus	2/3 (66.7)	1/1 (100.0)	3/3 (100.0)	1/1 (100.0)
Streptococcus constellatus	3/3 (100)	2/2 (100.0)	3/3 (100.0)	2/2 (100.0)
Streptococcus intermedius	9/11 (81.8)	6/7 (85.7)	8/11 (72.7)	6/7 (85.7)
Streptococcus dysgalactiae	0/0	2/2 (100.0)	0/0	2/2 (100.0)
Streptococcus pyogenes	6/6 (100)	12/14 (85.7)	5/6 (83.3)	12/14 (85.7)
				(b) (4)
Enterococcus faecalis	2/2 (100.0)	4/4 (100.0)	2/2 (100.0)	3/4 (75.0)
ME population				
Staphylococcus aureus	81/84 (96.4)	93/96 (96.9)	81/84 (96.4)	93/96 (96.9)
MRSA	26/27 (96.3)	38/40 (95.0)	26/27 (96.3)	38/40 (95.0)
MSSA	55/57 (96.5)	55/56 (98.2)	55/57 (96.5)	55/56 (98.2)
Streptococcus agalactiae	2/2 (100.0)	1/2 (50.0)	1/1 (100.0)	1/2 (50.0)
Streptococcus anginosus group	14/17 (82.4)	9/9 (100.0)	13/15 (86.7)	6/6 (100.0)
Streptococcus anginosus	1/1 (100.0)	0/0	2/2 (100.0)	0/0
Streptococcus constellatus	3/3 (100.0)	1/1 (100.0)	3/3 (100.0)	1/1 (100.0)
Streptococcus intermedius	8/10 (80.0)	5/5 (100.0)	8/10 (80.0)	5/5 (100.0)
Streptococcus dysgalactiae	0/0	2/2 (100.0)	0/0	2/2 (100.0)
Streptococcus pyogenes	5/5 (100.0)	12/13 (92.3)	5/5 (100.0)	12/13 (92.3)
				(b) (4)
Enterococcus faecalis	2/2 (100.0)	3/3 (100.0)	2/2 (100.0)	3/3 (100.0)

n = Number of patients with the respective observation; N = Number of microITT patients with the respective pathogen at baseline; MicroITT = Microbiological intent-to-treat; EOT = End of treatment; ME = Microbiologically evaluable at the respective clinic visit; MRSA = Methicillin-resistant *Staphylococcus aureus*; MRSA = Methicillin-sensitive *Staphylococcus aureus*.

***Enterococcus* species:**

A total of 17 patients had *Enterococcus* species isolated at baseline in the MicroITT population in study 303. A listing of these patients, infection type, dalbavancin MIC of the isolate and clinical response is presented in Table 35. The infection types in these patients were cellulitis, traumatic wound or major abscess. Most of these patients were from Europe. The clinical response rates at 48-72 hours and at end of therapy visit are shown in Table 36.

Table 35: Patients with *Enterococcus* species at baseline in the microITT population.

USUBJID	Organisms#	CE	Infection Type	Specimen Type	Treatment group	MIC	Region	CL RESP	CSEOT4
(b) (6)	*Enterococcus faecalis*	N	Major Abscess	ABSSSI	DALB1000 + 500	0.06	US	Clinical Responder	Clinical Success
	*Enterococcus faecium**	Y	Cellulitis	ABSSSI	DALB1000 + 500	0.06	US	Clinical Responder	Clinical Success
	*Enterococcus faecalis**	Y	Cellulitis	ABSSSI	DALB1000 + 500	0.03	Europe	Clinical Responder	Clinical Success
	Enterococcus faecium	N	Major Abscess	ABSSSI	DALB1500	0.12	Europe	Clinical Non-Responder	Clinical Success
	*Enterococcus faecalis**	Y	Traumatic Wound / Surgical Site Infection	ABSSSI	DALB1000 + 500	0.03	Europe	Clinical Responder	Clinical Success
	*Enterococcus faecalis**	Y	Traumatic Wound / Surgical Site Infection	ABSSSI	DALB1500	0.03	Europe	Clinical Responder	Clinical Success
	Enterococcus faecalis	Y	Cellulitis	ABSSSI	DALB1000 + 500	0.03	Europe	Clinical Responder	Clinical Success
	Enterococcus faecalis	N	Cellulitis	ABSSSI	DALB1000 + 500	0.06	Europe	Clinical Non-Responder	Clinical Success
	Enterococcus faecalis	Y	Traumatic Wound / Surgical Site Infection	ABSSSI	DALB1000 + 500	0.03	Europe	Clinical Responder	Clinical Success
	Enterococcus faecalis	Y	Cellulitis	ABSSSI	DALB1000 + 500	0.06	Europe	Clinical Responder	Clinical Success
	*Enterococcus faecalis**	Y	Cellulitis	ABSSSI	DALB1000 + 500	0.03	Europe	Clinical Non-Responder	Clinical Success
	*Enterococcus faecalis**	Y	Cellulitis	ABSSSI	DALB1000 + 500	0.03	Europe	Clinical Responder	Clinical Success
	*Enterococcus faecium**	Y	Traumatic Wound / Surgical Site Infection	ABSSSI	DALB1500	0.03	Europe	Clinical Responder	Clinical Failure
	Enterococcus faecalis	Y	Major Abscess	ABSSSI	DALB1500	0.06	Europe	Clinical Responder	Clinical Success
	Enterococcus faecalis	N	Cellulitis	ABSSSI	DALB1500	0.03	Europe	Clinical Responder	Clinical Success
	*Enterococcus faecalis**	Y	Cellulitis	ABSSSI	DALB1500	0.06	Europe	Clinical Responder	Clinical Success
	Enterococcus faecalis	N	Cellulitis	ABSSSI	DALB1000 + 500	0.06	Other	Clinical Responder	Clinical Success

* Monoinfection with pathogen, # all isolates were susceptible to vancomycin, CLRESP = clinical response at 48-72 hours, CSEOT4 = clinical status at EOT, CE = clinically evaluable population at EOT, MIC = dalbavancin miimum inhibitory concentration

Table 36: Clinical response in patients with baseline *Enterococcus* species

Organisms	**MicroITT (48-72 hours) n/N(%)**		**ME- EOT n/N(%)**		**ME- FU n/N(%)**	
	DALB 1000 + 500	**DALB 1500**	**DALB 1000 + 500**	**DALB 1500**	**DALB 1000 + 500**	**DALB 1500**
E. faecalis	8/10 (80.0)	4/4 (100.0)	7/7 (100.0)	3/3 (100.0)	6/7 (85.7)	3/3 (100.0)
E. faecium	1/1 (100.0)	1/2 (50.0)	1/1(100.0)	0/1 (0.0)	1/1(100.0)	0/1 (0.0)

Bacteremia:
Bacteremia was associated with ABSSSI in 20 patients in the MicroITT population (DALB 1000+500; n = 10; DALB 1500, n = 10; see Table 37). All of the patients with follow-up cultures had cleared the bacteremia at EOT. One patient in the single-dose group who had Gram-positive bacteremia at baseline (b) (4) had no follow-up blood cultures available for evaluation, but was a clinical success at Day 14 and Day 28.

Table 37: Patients with bacteremia at baseline in the two treatment groups in study DUR001-303.

Baseline Pathogen*	**Dalbavancin Treatment Group, n/N (%)**	
	EOT Visit	
	Single-dose (1500 mg)	**Two-doses (1000 mg + 500 mg)**
MITT population		
Staphylococcus aureus	8/8 (100)	7/7 (100)
MRSA	1/1 (100)	3/3 (100)
MSSA	7/7 (100)	4/4 (100)
Streptococcus pyogenes	1/1 (100)	2/2 (100)
Gemella morbillorum	0/0	1/1 (100)
Propionibacterium acnes	1/1 (100.0)	0/0
ME population		
Staphylococcus aureus	8/8 (100)	6/6 (100)
MRSA	1/1 (100)	2/2 (100)
MSSA	7/7 (100)	4/4 (100)
Streptococcus pyogenes	0/0	1/1 (100)
Gemella morbillorum	0/0	1/1 (100)
Propionibacterium acnes	1/1 (100.0)	0/0

MicroITT = Microbiological intent-to-treat; EOT = End of treatment; ME = Microbiologically evaluable at the respective clinic visit; n = Number of patients with the respective observation; N = Number of microITT patients (percentages are calculated using as denominator the number of microITT patients with the respective pathogen at baseline); MRSA = Methicillin-resistant *Staphylococcus aureus;* MSSA = Methicillin-sensitive *S. aureus*.

MIC distribution:
The baseline MIC range, MIC_{50}s and MIC_{90}s of dalbavancin in the single dose and the two-dose arms for key target baseline pathogens are summarized in Table 38. Analysis was performed on the MicroITT population.

Table 38. DUR001-303: MIC Summary for Baseline Gram-Positive Pathogens (MicroITT Population).

Organism	N*	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
All species	415	≤0.001-0.12	0.06	0.06
Dalbavancin (1 dose)	204	≤0.001-0.12	0.06	0.06
Dalbavancin (2 dose)	211	≤0.001-0.12	0.06	0.06
Staphylococcus aureus	292			
Dalbavancin (1 dose)	142	0.03-0.12	0.06	0.06
Dalbavancin (2 dose)	150	0.015-0.12	0.06	0.06
MRSA	91			
Dalbavancin (1 dose)	35	0.03-0.06	0.06	0.06
Dalbavancin (2 dose)	56	0.015-0.06	0.06	0.06
MSSA	201			
Dalbavancin (1 dose)	107	0.03-0.12	0.06	0.06
Dalbavancin (2 dose)	94	0.03-0.12	0.06	0.06
Staphylococcus haemolyticus	3			
Dalbavancin (1 dose)	2	0.03	--	--
Dalbavancin (2 dose)	1	0.06	--	--
Streptococcus pyogenes	36			
Dalbavancin (1 dose)	14	0.004-0.015	.004	0.015
Dalbavancin (2 dose)	22	0.004-0.03	0.015	0.015
Streptococcus agalactiae	12			
Dalbavancin (1 dose)	6	0.008-0.015	--	--
Dalbavancin (2 dose)	6	0.008-0.015	--	--
Streptococcus dysgalactiae	7			
Dalbavancin (1 dose)	4	0.008	--	--
Dalbavancin (2 dose)	3	0.008	--	--
Streptococcus anginosus	8			
Dalbavancin (1 dose)	6	0.001-0.008	--	--
Dalbavancin (2 dose)	2	0.004-0.008	--	--
Streptococcus constellatus	16			
Dalbavancin (1 dose)	10	0.004-0.03	0.008	0.008
Dalbavancin (2 dose)	6	0.004-0.03	--	--
Streptococcus intermedius	23			
Dalbavancin (1 dose)	14	0.001-0.008	0.001	0.008
Dalbavancin (2 dose)	9	0.001-0.008	--	--
Streptococcus anginosus group	1			
Dalbavancin (1 dose)	0	--	--	--
Dalbavancin (2 dose)	1	0.004	--	--
Enterococcus faecium.	3			
Dalbavancin (1 dose)	2	0.03-0.12	--	--
Dalbavancin (2 dose)	1	0.06	--	--
Enterococcus faecalis.	14			
Dalbavancin (1 dose)	4	0.03-0.06	--	--
Dalbavancin (2 dose)	10	0.03-0.06	0.03	0.06

Reference: CSR DUR001-303, Table14.1.18.1.

* Includes only those isolates that were sent to the central microbiology laboratory for MIC determination.

QC Strains

For study DUR001-303, *S. aureus* ATCC 29213 was tested 16 times (MIC range 0.03-0.06 µg/mL), *E. faecalis* ATCC 29212 was tested 4 times (MIC range 0.06 µg/mL) and *S. pneumoniae* ATCC 49619 was tested 22 times (MIC range 0.008-0.03 µg/mL) and were within the range described by CLSI.

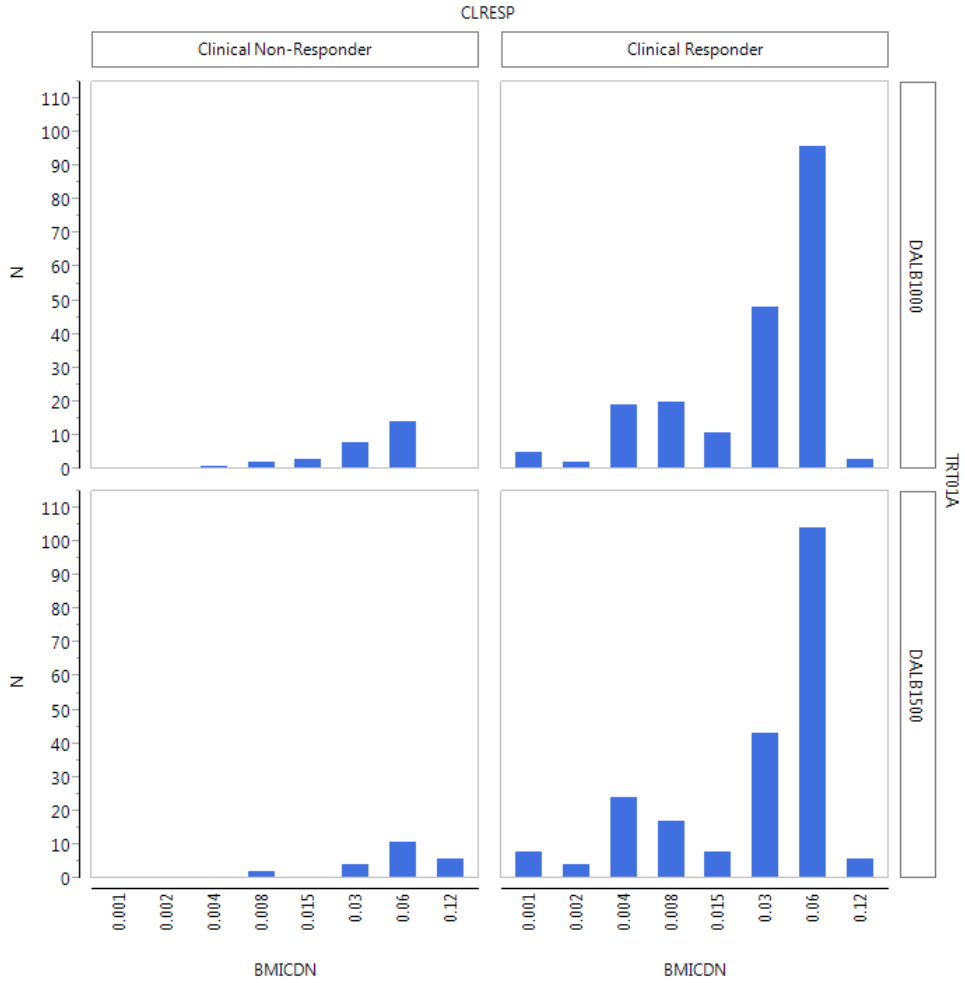
Reviewer comment:

All isolates in study DUR001-303 had dalbavancin MIC ≤0.12 µg/mL. The dalbavancn MIC_{90} values for *S. aureus*, *S. pyogenes*, *S. anginosus* group and *E. faecalis* were ≤0.06 µg/mL. No post-baseline isolates with increase in dalbavancin MIC (≥4 fold increase in MIC value) were observed in this study.

Correlation between dalbavancin MIC of baseline isolate and clinical outcome.

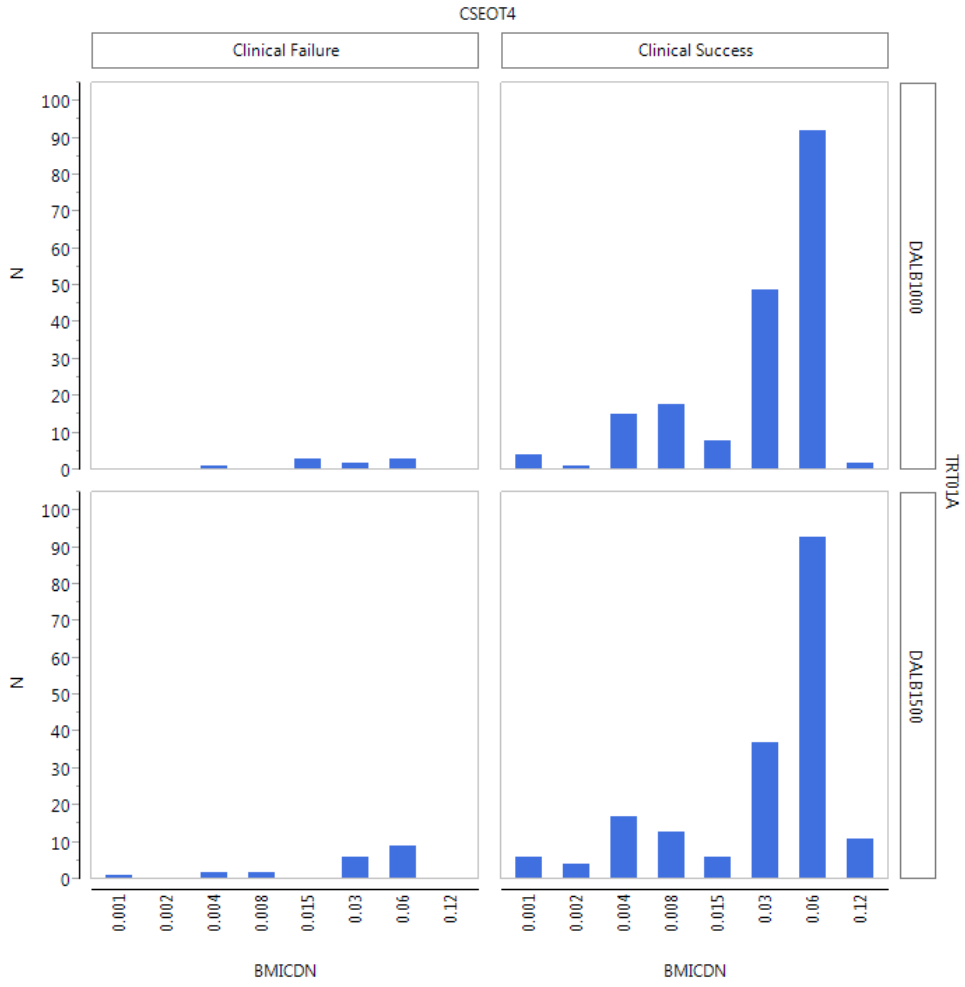
The microITT and ME populations were used to analyze the correlation between dalbavancin MIC and clinical outcome (Figures 4 and 5).

Figure 4: Correlation of baseline dalbavancin MIC with clinical response at 48-72 hours in the microITT population.



CLRESP = clinical response at 48-72 hours; TR101A = actual treatment group;
BMICDN = baseline dalbavancin MIC for isolate.

Figure 5: Correlation of baseline dalbavancin MIC with clinical success at EOT in the ME-population.



CLEOT4 = clinical success at end of therapy
TR101A = actual treatment group
BMICDN = baseline dalbavancin MIC for isolate.

Reviewer comment:
No correlation was observed between baseline dalbavancin MIC and clinical outcome in the two treatment groups.

Pooled phase 3 clinical studies DUR001-301, DUR001-302, DUR001-303:
Analysis on pooled data from previously completed phase 3 studies, DUR001-301 and DUR001-302 and the new study DUR001-303 were performed to determine the clinical success rates for by baseline pathogens in all patients treated with dalbavancin (single dose or two-dose regimens). This analysis was used to generate the pathogen list in the microbiology subsection of the package insert. The DUR001-301 and DUR001-302 studies evaluated two doses of

dalbavancin (1000 mg IV on day 1 and 500 mg IV on day 8) compared to vancomycin, with the possibility of switching to oral linezolid in the comparator arm. The primary efficacy outcome in these 2 studies was clinical response (cessation of spread and absence of fever) at 48-72 hours post treatment in the ITT population. The secondary outcomes in these two studies included clinical efficacy at end of treatment by pathogen, clinical and microbiological outcomes by patient, and pathogen eradication rates in the two treatment groups. Patients also had short-term and long-term follow-up visits. The successful response by pathogen outcomes included eradication and presumed eradication. In these studies, pathogen eradication was often presumed based on clinical response. Studies DUR001-301 and DUR001-302 were reviewed previously (Please see review dated February 20, 2014 by Dr. Peter Coderre). Only pooled data from the 3 studies are included here. The study DUR001-303 did not assess microbiological outcomes.

Clinical responses at various time-points by pathogen were analyzed for the pooled ABSSSI data sets using the microITT and ME-EOT populations (Table 39). Please note that (b) (4) is not considered as a pathogen for this indication.

Table 39: Clinical success by baseline pathogens in pooled DUR001-301, DUR001-302, DUR001-303 studies.

Baseline pathogen*	**48-72 hours n/N(%)**		**Day 14 (EOT) n/N(%)**		**Day 28 (Final Visit) n/N(%)**	
	Clinical responder (MITT)		**Clinical success (ME)**		**Clinical success (ME)**	
	Dalbavancin	**Comparator**	**Dalbavancin**	**Comparator**	**Dalbavancin**	**Comparator**
S. aureus	496/553 (89.7%)	232/256 (90.6)	453/483 (93.8)	204/215 (94.9)	439/483 (90.9)	203/211(96.2)
MRSA	162/187 (86.6)	59/67 (88.1)	152/162 (93.8)	53/55 (96.4)	148/162 (91.4)	53/55 (96.4)
MSSA	334/366 (91.3)	173/189 (91.5)	301/321(93.8)	151/160 (94.4)	291/321(90.7)	150/156 (96.2)
S. pyogenes	64/73 (87.7)	27/36 (75.0)	60/65 (92.3)	28/32 (87.5)	60/65 (92.3)	29/32 (90.6)
S. agalactiae	20/24(83.3)	10/14 (71.4)	14/18 (77.7)	6/7 (85.7)	15/18 (83.3)	6/7 (85.7)
S. dysgalactiae	10/10 (100.0)	1/1(100.0)	8/9 (88.8)	1/1 (100.0)	8/9 (88.9)	1/1 (100.0)
S. anginosus group	76/79 (96.2)	27/27 (100.0)	58/65 (89.2)	22/22 (100.0)	61/65 (93.8)	21/22 (95.5)
S. anginosus	14/14 (100.0)	4/4 (100.0)	11/12 (91.7)	3/3 (100.0)	12/12 (100.0)	3/3 (100.0)
S. constellans	30/32 (93.8)	16/16 (100.0)	22/24 (91.7)	14/14 (100.0)	24/24 (100.0)	13/14 992.9)
S. intermediate	32/33 (96.9)	7/7 (100.0)	25/29 (86.2)	5/5 (100.0)	25/29 (86.2)	5/5 (100.0)
(b) (4)						
E. faecalis	24/26 (92.3)	12/13 (92.3)	19/19 (100.0)	5/5(100.0)	18/19 (94.7)	5/5 (100.0)

*Includes isolates from mixed infections.

Reviewer comment:
The applicant would like to include *Streptococcus dysgalactiae*, (b) (4) *Enterococcus faecalis* (vancomycin-susceptible isolates only) in the first list of microorganisms against which dalbavancin is active *in vitro* and in clinical studies in the MICROBIOLOGY section of the label. Based on the results from the pooled studies shown above, *Streptococcus dysgalactiae and Enterococcus faecalis* (vancomycin-susceptible isolates only) can be included in the first list provided there are no changes to PK parameters based on single dosing of 1500 mg IV compared to two doses of 1000 mg followed by 500 mg IV dalbavancin. Please note that (b) (4) is not considered as a pathogen for this indication.

MIC distribution:
The MIC distribution for all isolates in the microITT population of the pooled dataset for studies DUR001-301, DUR001-302, DUR001-303 is shown in Table 40. The dalbavancin MIC range for baseline isolates in the 3 studies ranged from 0.001 to 0.25 μg/mL. The dalbavancin MIC_{90}

values for all isolates were 0.06 μg/mL. The MIC distribution is similar to that observed in surveillance studies.

Table 40. Dalbavancin MIC Distributions for the Key Baseline Pathogens across ABSSSI Studies (Appended from submission).

Pathogen	MIC (μg/mL)	Number of Isolates, MicroITT Population, Both Arms	
		DUR001-303	DUR001-301 + DUR001-302+DUR001-303
Staphylococcus aureus (All)			
	0.008	0	0
	0.015	2	6
	0.03	78	178
	0.06	202	356
	0.12	10	15
	0.25	0	1
MRSA			
	0.008	0	0
	0.015	2	2
	0.03	23	67
	0.06	66	107
	0.12	0	1
	0.25	0	1
MSSA			
	0.015	0	4
	0.03	55	111
	0.06	136	249
	0.12	10	14
	0.25	0	0
S. pyogenes	≤0.001	0	1
	0.002	0	2
	0.004	22	31
	0.008	8	17
	0.015	5	22
	0.03	1	4
	0.06	0	2
	0.12	0	3
	0.25	0	0
S. agalactiae			
	≤0.001	0	1
	0.008	4	7
	0.015	8	13
	0.03	0	5
	0.06	0	1
	0.12	0	0
	0.25	0	0

Table 40. Dalbavancin MIC Distributions for Key Baseline Pathogens across ABSSSI Studies (Continued) (Appended from submission).

Pathogen	MIC (µg/mL)	Number of Isolates, MicroITT Population, Both Arms	
		DUR001-303	DUR001-301 + DUR001-302+DUR001-303
Streptococcus anginosus Group[a]			
	≤0.001	0	12
	0.002	0	10
	0.004	1	16
	0.008	0	24
	0.015	0	6
	0.03	0	3
	0.06	0	1
	0.12	0	0
	0.25	0	0
Streptococcus anginosus			
	≤0.001	1	1
	0.002	0	1
	0.004	5	7
	0.008	2	4
	0.015	0	0
	0.03	0	0
	0.06	0	0
	0.12	0	0
	0.25	0	0
Streptococcus constellatus			
	≤0.001	0	0
	0.002	0	0
	0.004	4	7
	0.008	10	14
	0.015	0	5
	0.03	2	3
	0.06	0	1
	0.12	0	0
	0.25	0	0

Table 40. Dalbavancin MIC Distributions for Key Baseline Pathogens across ABSSSI Studies (Continued) (Appended from submission)..

Pathogen	MIC (µg/mL)	Number of Isolates, MicroITT Population, Both Arms	
		DUR001-303	DUR001-301 + DUR001-302+DUR001-303
Streptococcus intermedius			
	≤0.001	11	11
	0.002	6	9
	0.004	2	2
	0.008	4	6
	0.015	0	1
	0.03	0	0
	0.06	0	0
	0.12	0	0
	0.25	0	0
Streptococcus dysgalactiae			
	≤0.001	0	0
	0.002	0	0
	0.004	0	0
	0.008	7	7
	0.015	0	0
	0.03	0	0
	0.06	0	0
	0.12	0	0
	0.25	0	0
Enterococcus faecalis			
	≤0.001	0	0
	0.002	0	0
	0.004	0	0
	0.008	0	0
	0.015	0	1
	0.03	8	14
	0.06	6	9
	0.12	0	0
	0.25	0	0

[a] Includes *S. anginosus* (8), *S. constellatus* (29), *S. intermedius* (12). In studies DUR001-301, DUR001-301 and DUR001-303, *S. anginosus* group streptococci were speciated as *S. constellatus*, *S. anginosus* and *S. intermedius* except for one isolate (DUR001-303) that was speciated as "*S. anginosus* group".DUR001-303 CSR Table: 14.1.16.1 and ISM Table 4.1.

QC strains studies DUR001-301 and DUR001-302:
For the studies DUR001-301 and DUR001-302, *S. aureus* ATCC 29213 was tested 94 times (modal MIC 0.03 µg/mL), *E. faecalis* ATCC 29212 was tested 20 times (MIC range 0.03-0.06 µg/mL) and *S. pneumoniae* ATCC 49619 was tested 61 times (MIC range 0.008-0.03 µg/mL and the MICs were within the range described by CLSI.

Other methods of dalbavancin susceptibility testing:

At present dalbavancin disks are not available and are not recommended for use in susceptibility testing due to poor diffusion of the drug out of the disk into the agar. An Etest for dalbavancin susceptibility testing was developed by bioMérieux. This method was validated against the broth microdilution method of MIC determination (Fritsche 2006)[23]. A total of 200 gram-positive isolates including *Staphylococcus aureus* (90 total, including 40 MRSA and 5 displaying reduced susceptibility to vancomycin [MICs, 4 to 8 μg/ml]), coagulase-negative staphylococci (CoNS) (20 total; 10 methicillin-resistant), *Enterococcus* spp. (20 total; 5 *Enterococcus faecalis*, 9 *Enterococcus faecium*, 6 others;14 vancomycin-resistant), beta-hemolytic streptococci (*n* = 37), *Streptococcus pneumoniae* (*n* = 20), and viridans group streptococci (*n* =13) were tested. MIC values determined by the Etest for the QC strains were within the CLSI QC range (established for broth microdilution) in five replicate tests. Additionally, Etest MICs for the 200 clinical isolates were all within ±2 $\log_2$ dilution steps (92.5% within one dilution) of the broth microdilution MICs. However, only 80% overall essential agreement between Etest and MIC were observed in recent studies. The MICs are not easy to read as thin ellipses are obtained and some production batches yielded MICs outside the CLSI range for *E. faecalis* isolates. The Etest is being redeveloped (Etest DAL32/ Durata Study Report)[24]. The dalbavancin Etest is not approved by CDRH.

Other analysis:

In the phase 3 studies (DUR001-301, DUR001-302 and DUR001-303), the baseline *S. aureus* isolates were tested for the presence of Panton-Valentine leukocidin (PVL) using a multiplex real time polymerase chain reaction (PCR) method (McDonald 2005)[25]. In study DUR001-303, PVL was present in the majority of MRSA isolates (31 of 34, 91.2%) and was also present in nearly one-third of MSSA isolates (42 of 125, 33.6%) in the microITT population. All MRSA isolates were positive for the presence of mecA.

5 BREAKPOINT DETERMINATION:

The current approved susceptibility interpretive criterion for dalbavancin is ≤0.12 μg/mL for the following organisms:
Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus pyogenes,
Streptococcus agalactiae, and
Streptococcus anginosus group

[23] Fritsche TR, Rennie RP, Goldstein BP, Jones RN. Comparison of dalbavancin MIC values determined by Etest (AB BIODISK) and reference dilution methods using gram-positive organisms. J Clin Microbiol. 2006;44:2988-90.
[24] Etest DAL32/Durata Study
[25] McDonald RR, Antonishyn NA, Hansen T et al. Development of a Triplex Real-Time PCR Assay for Detection of Panton-Valentine Leukocidin Toxin Genes in Clinical Isolates of Methicillin-Resistant *Staphylococcus aureus*. J. Clin. Microbol. 2005; 6147-6149.

The sponsor has proposed the following changes to the breakpoint based on a revised population PK model including projected target attainment, data from the new neutropenic mouse model PK/PD study, and MIC distribution data from clinical and surveillance studies (Table 41).

Table 41. Susceptibility Test Interpretive Criteria for Dalbavancin (Appended from the submission).

Pathogen	MIC (mcg/mL)[a]			Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤ (b) (4)	--	--	--	--	--
Streptococcus pyogenes, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, (b) (6) *Streptococcus anginosus* group	≤	--	--	--	--	--
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤	--	--	--	--	--

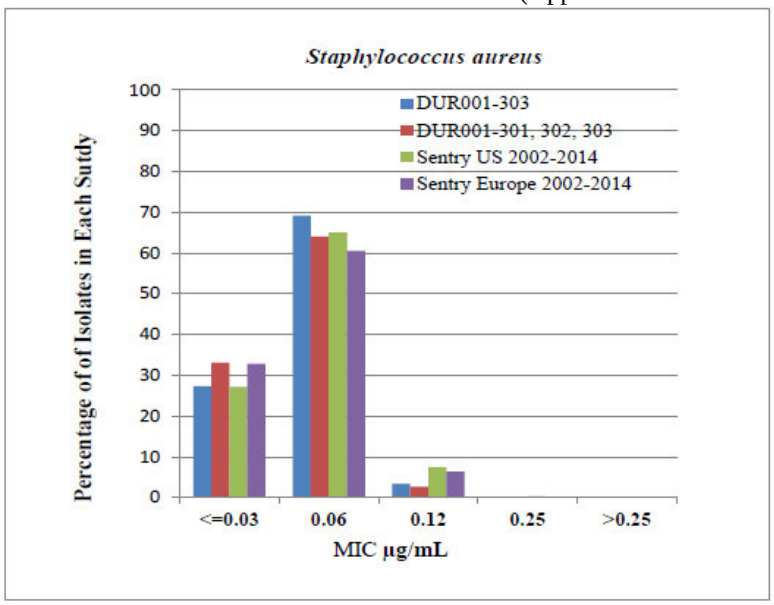
[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". (b) (4)

5.1 MIC distribution for surveillance and clinical isolates

S. aureus:

The US and EU surveillance data for 2002-2014 included >80,000 *S. aureus* isolates. The dalbavancin MIC distribution was unimodal and similar in clinical and surveillance studies (Figure 6). The dalbavancin MIC ranges in the clinical studies (≤0.015 to 0.25 µg/L) overlapped with that observed in surveillance studies (≤0.03 to 0.5 µg/mL). In DUR001-301 and DUR001-302, there was one isolate at 0.25 µg/mL in the dalbavancin arm. However, this isolate reverted to MIC of 0.06 µg/mL, when it was re-tested. In the SENTRY surveillance study, there were a few isolates at MIC 0.25 µg/mL and (b) (4) µg/mL (data not shown). For *S. aureus* the dalbavancin MIC_{90} in both clinical and surveillance studies was 0.06 µg/mL. The dalbavancin MIC distribution for MRSA isolates were same as that for all *S. aureus* isolates. Two non-susceptible *S. aureus* isolates (MIC=0.25 µg/mL) were obtained from 2014 surveillance study. The dalbavancin MIC value for both of the isolates was 0.06 µg/mL upon retesting.

Figure 6. Dalbavancin MIC Distributions: *S. aureus* from DUR001-001, DUR-001-002 and DUR001-003 ABSSSI and Surveillance Studies (Appended from submission).



***Streptococcus* spp:**

The dalbavancin MIC distributions for ABSSSI *S. pyogenes* isolates from the surveillance program in the U.S. and Europe (2002-2014 SENTRY) are compared with results from the DUR001-301, DUR001-302 and DUR001-303 clinical trials in Figure 7. Similar distributions for *S. agalactiae* and *S. dysgalactiae* are shown in Figures 8 and 9.

Figure 7. Dalbavancin MIC Distributions: *S. pyogenes* from DUR001-301, DUR001-302 and DUR001-303 ABSSSI and Surveillance Studies (Appended from submission).

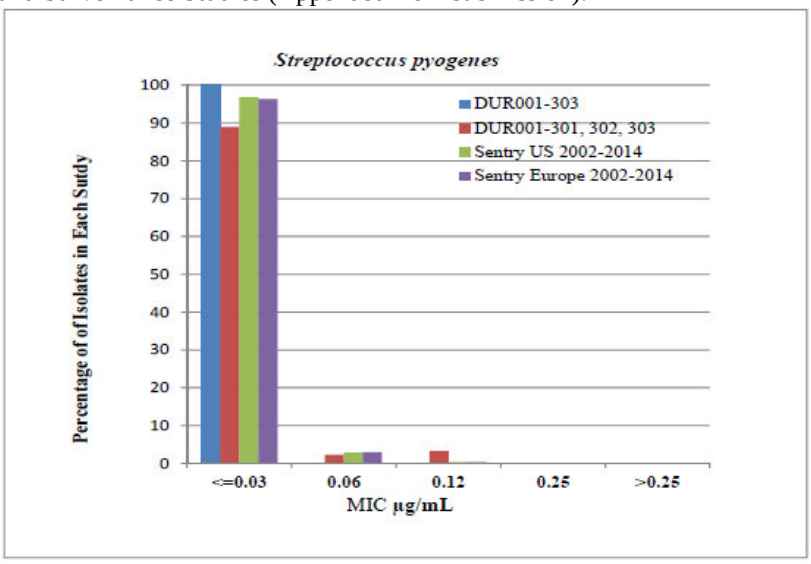


Figure 8. Dalbavancin MIC Distributions: *S. agalactiae* from DUR001-301, DUR001-302 and DUR001-303 ABSSSI and Surveillance Studies (Appended from submission).

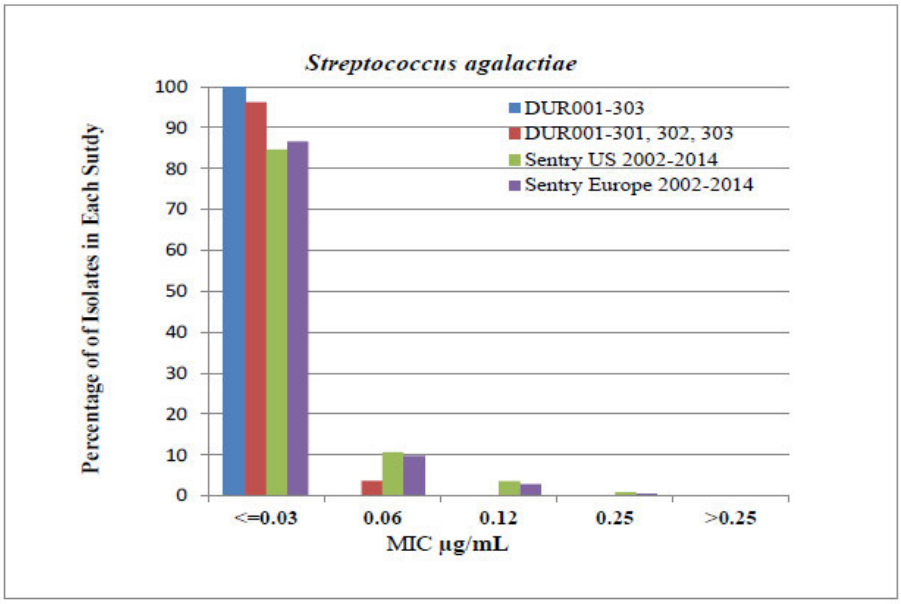
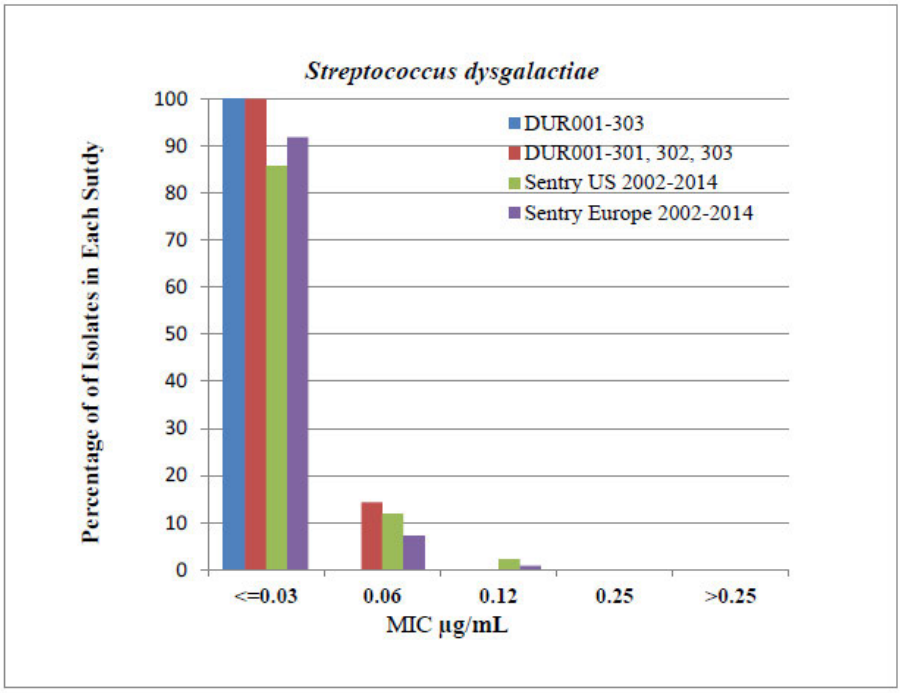


Figure 9. Dalbavancin MIC Distribution: *S. dysgalactiae* Isolates from the DUR001-301, DUR001-302 and DUR001-303 ABSSSI and Surveillance Studies (Appended from the submission).

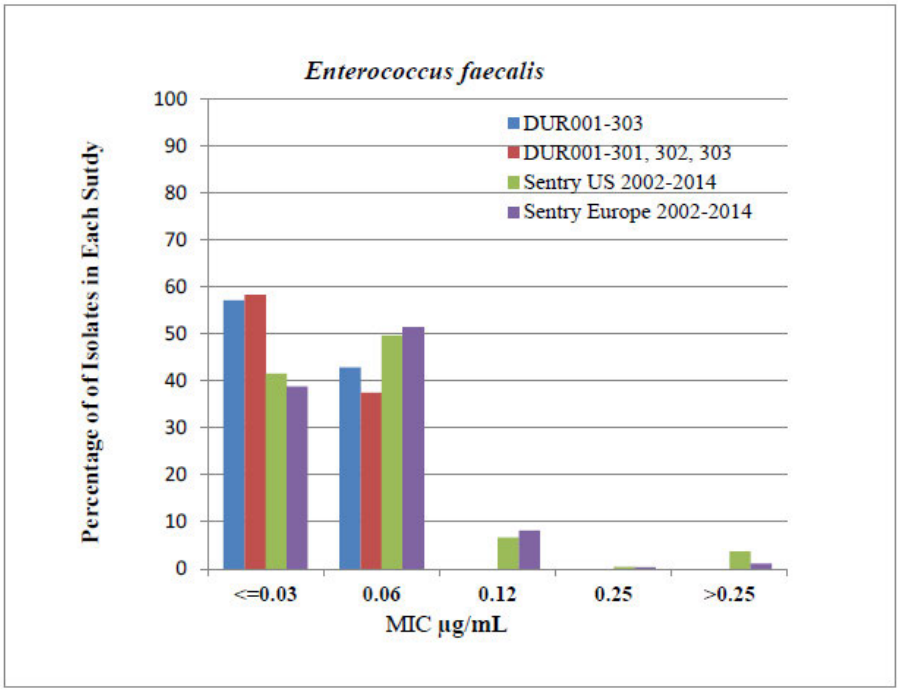


The dalbavancin MIC_{90} for *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, (b) (4) *and S. anginosus group* were ≤ 0.06 µg/mL (Figures 7, 8, 9 and Tables 14, 15, 38 and 40).

***Enterococcus* Species:**

The dalbavancin MIC distributions for ABSSSI *E. faecalis* isolates from the surveillance program in the U.S. and Europe (2002-2014 SENTRY) are compared with results from the DUR001-301, DUR001-302 and DUR001-303 clinical trials in Figure 10. The dalbavancin MIC_{90} for *E. faecalis* were 0.06 to 0.12 μg/mL in the recent years (Figure 10, Tables 38 and 40). A second population appears to develop at MICs>0.25 μg/mL, suggesting a bimodal distribution. However, there is insufficient number of vancomycin susceptible *E. faecalis* with dalbavancin MIC>0.25 μg/mL in these studies.

Figure 10. Dalbavancin MIC Distribution: *E. faecalis* Isolates from the DUR001-301, DUR001-302 and DUR001-303 (Appended from the submission).



In summary, clinical trial and surveillance data for *S. aureus* including methicillin resistant isolates, *S. pyogenes, S. agalactiae, S. dysgalactiae, Viridans Group Streptococci* and *E. faecalis* showed similar MIC distributions. The dalbvancin MIC_{90} for all isolates were ≤ 0.12 μg/mL.

5.2 Clinical studies:

The clinical outcome data for isolates with dalbavancin MICs > 0.25 μg/mL were available for only two patients in the DUR001-301 and 302 studies. In DUR001-303, there were no patients with MICs ≥ 0.25 μg/mL. The MIC values for the non-susceptible isolates from studies DUR001-301 and DUR001-302 isolates retested at 0.06 μg/mL. These findings led to retesting of isolates from 2011-2013 surveillance studies with dalbavancin MICs above the breakpoint including 40 isolates of *S. aureus*, 38 isolates of *S. agalactiae* and 1 isolate of *S. dysgalactiae*. Of the surveillance organisms, 70 out of 79 (88.6%) retested at or below the dalbavancin breakpoint of ≤ 0.12 μg/mL (Table 42) (Report 15-DUR-02)[2]. At present, >99.9% of *S. aureus* isolates are

wild type organisms and have a unimodal MIC distribution. The applicant states that in a clinical setting, a hospital clinical microbiology laboratory would not feel compelled to retest an organism that is non-susceptible. This would result in difficulty for device manufacturers to obtain categorical agreement. The sponsor has proposed to update the label with the following statement as footnote to the susceptibility interpretive criteria Table (b) (4) in the package insert. (b) (4) Alternatively, the applicant states that increasing the breakpoint to (b) (4) µg/mL could resolve the testing issues.

Table 42. 2011-2013 Dalbavancin Surveillance MIC Retesting Results for *S. aureus*, *S. agalactiae* and Group G streptococci (Appended from the submission).

Organism (total number of isolates in study)	Number of Isolates re-tested	Original Results[a] (number of isolates at each MIC value)	Retesting Results (number of isolates at each MIC value)
S. aureus (20,501)[b]	40	0.25 (36)-0.5 (4)	0.03 (2), 0.06 (24), 0.12 (5), 0.25 (4), >0.25 (5)
S. agalactiae (1,347)	38	0.25 (38)	0.015 (32), 0.03 (5), 0.06 (1)
Group G Streptococci (204)[c]	1	0.25 (1)	0.06 (1)

[a] Isolates tested and retested at JMI Laboratories, North Liberty, IA US
[b] One isolate was re-identified as *S. haemolyticus*
[c] Isolate was re-identified as *S. dysgalactiae*

Reviewer comment:
Please note that (b) (4) is not considered as a pathogen for this indication. There is extremely limited clinical data for patients with infections due to baseline isolates with dalbavancin MIC of ≥ 0.25 µg/mL. There was no correlation between clinical outcome and MIC values in the clinical studies. There is no clinical data to support the breakpoint of (b) (4) µg/mL for *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus dysgalactiae,* and *Streptococcus anginosus* group, and *Enterococcus faecalis* (vancomycin-susceptible isolates only). The MIC_{90} values for all pathogens in the clinical studies and surveillance studies were ≤ 0.12 µg/mL. Upon retesting of isolates at the lower end of the MIC distribution, the MIC shifted towards the modal MIC for the species tested. Only few (20%) of the non-susceptible isolates with MICs ≥ 0.25 µg/mL remained non-susceptible. Retesting of isolates at the central laboratory is useful to monitor development of resistance. Retesting of isolates at the local laboratory may be useful only if it is used to guide therapy. The applicant did not state this to be the reason for retesting at the local laboratory. Isolates yielding test results other than "Susceptible" should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for additional testing

In vitro studies show that dalbavancin MIC_{90} against *S. aureus* VISA isolates is 1 µg/mL. These isolates have changes to the cell wall. Also, small frequencies of sub-clones of *S. aureus* VISA isolates grew on agar with 2 µg/mL of dalbavancin. From these studies, it appears that a dalbavancin MIC of 1-2 µg/mL may correspond with resistance development. The dalbavancin MIC_{90} for vancomycin resistance *E. faecalis* isolates was ≥ 4 µg/mL in the US and >0.25 in Europe.

5.3 ECOFF calculations:

The National Antimicrobial Susceptibility Testing Committee for the United States, USCAST, has posted on their website a resistance breakpoint of ≥0.25 μg/mL for *Staphylococcus aureus*, β-hemolytic *Streptococcus* and Viridans Group *Streptococcus* by inference from vancomycin susceptibility. ECOFF calculations for *Staphyloccus aureus* and *Streptococcus agalactiae* suggest a breakpoint of 0.12 μg/mL as these do not exhibit resistance phenotype[26].

5.4 Pharmacokinetic/Pharmacodynamic PK-PD analysis:

Previous animal studies suggested that the neutropenic mouse thigh model was appropriate for PK-PD analysis. Study VER001-MI-013 (reviewed in the original NDA) and new study (DAL-MC-01) determined free drug AUC/MIC of the infecting organisms to be the appropriate parameter for PK-PD analysis. The free drug AUC/MIC ratio target attainment of 1000 for *S. aureus* and 100 for *Streptococcus* species was determined from the neutropenic mouse thigh model studies. *Enterococcus* species were not tested in the animal models.

Monte Carlo simulations were performed using the target attainment ratios for free dalbavancin AUC/MIC. The binding of dalbavancin to protein in human and mouse plasma was taken into account in the modeling. The MIC distribution for *S. aureus* and *Streptococcus* spp. (MIC range 0.015 to 0.12 μg/mL) from three SSTI studies (VER001-8, VER001-9 and VER001-16) were used for the simulations along with higher simulated MIC distributions. These simulations suggested a > 93% probability of target attainment for a population of *S. aureus* with an MIC distribution where the MIC_{90}=1 μg/ml. For streptococci, the target attainment rates were > 90% for all parameters (T>MIC, AUC∞/MIC and AUC14 day/MIC) against populations with theoretical MICs ≤ 4μg/mL. The applicant provided a comparison of the target attainment for single 1500 mg IV dalbavancin dose and two dose dalbavancin regimen using the new and old animal PK-PD study (Tables 43 and 44).

Table 43: Target attainment for 1500 mg dose (old stasis target 265 hours; new stasis target 27.1 hours)..

MIC (mg/L)	New Target Attainment (%)	Old Target Attainment (%)
0.001	100.00	100.00
0.002	100.00	100.00
0.004	100.00	100.00
0.008	100.00	100.00
0.015	100.00	100.00
0.030	100.00	100.00
0.060	100.00	100.00
0.120	100.00	100.00
0.250	100.00	99.60
0.500	100.00	64.50
1.000	100.00	2.70
2.000	99.80	0.00
4.000	87.70	0.00
8.000	6.20	0.00
16.000	0.20	0.00

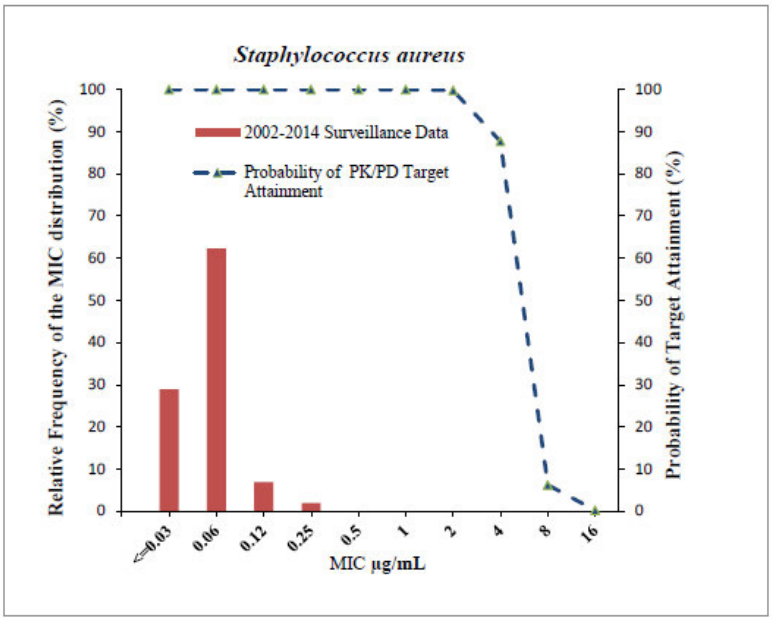
[26] European Committee on Antimicrobial Susceptibility Testing. Data from the EUCAST MIC distribution website, last accessed October 18,2015 ". http://www.eucast.org"

Table 44: Target attainment for 1000 mg dose (old stasis target 265 hours; new stasis target 27.1 hours)..

MIC (mg/L)	New Target Attainment (%)	Old Target Attainment (%)
0.001	100.00	100.00
0.002	100.00	100.00
0.004	100.00	100.00
0.008	100.00	100.00
0.015	100.00	100.00
0.030	100.00	100.00
0.060	100.00	100.00
0.120	100.00	99.88
0.250	100.00	91.20
0.500	100.00	8.76
1.000	100.00	0.14
2.000	98.05	0.00
4.000	29.37	0.00
8.000	0.62	0.00
16.000	0.00	0.00

Results of the simulation suggest that for both dosing regimens in DUR001-303, a >90% of simulated subjects would be expected to achieve the non-clinically derived stasis target at MIC <2 µg/mL (Figure 11).

Figure 11. Probability of PK-PD Target Attainment 1500 mg dose by Dalbavancin MIC against *S. aureus* for Non-Clinical Targets, Overlaid on the Dalbavancin MIC Distribution against *S. aureus* from 2002-2014 Surveillance Data.



Review comment:

The applicant states that target attainment for stasis is the most applicable for ABSSSI infection. Please see Clinical Pharmacology Review for target attainment analysis (stasis, 1-log kill, 2-log kill) e used for proposed breakpoint. The target attainment for both doses simulated using the old and new animal PK/PD study data supports a breakpoint of 0.25 µg/mL.

Overall, the clinical microbiology data support a susceptible breakpoint of 0.12 μg/mL for *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*), *Enterococcus faecalis* (vancomycin-susceptible isolates only) based on *in vitro* MIC distributions of isolates from clinical studies and surveillance. The non-clinical and clinical PK/PD target attainment analyses support a susceptible breakpoint of 0.25 μg/mL..

6 APPLICANT'S PROPOSED MICROBIOLOGY SUBSECTION OF THE PACKAGE INSERT

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dalbavancin is an antibacterial drug (b) (4) *(12.4)]*.

12. (b) (4) Microbiology

Mechanism of Action

Dalbavancin, a semisynthetic lipoglycopeptide, interferes with cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking. Dalbavancin is bactericidal *in vitro* against *Staphylococcus aureus* and *Streptococcus pyogenes* at concentrations similar to those sustained throughout treatment in humans treated according to the recommended dosage regimen.

Mechanism of Resistance

The development of bacterial isolates resistant to dalbavancin has not been observed, either *in vitro*, in studies using serial passage, or in animal infection experiments.

Interaction with Other Antimicrobials

When tested *in vitro*, dalbavancin demonstrated synergistic interactions with oxacillin and did not demonstrate antagonistic or synergistic interactions with any of the following antibacterial agents of various classes: gentamicin, vancomycin, levofloxacin, clindamycin, quinupristin/dalfopristin, linezolid, aztreonam, rifampin or daptomycin. The clinical significance of these *in vitro* findings is unknown.

Dalbavancin has been shown to be active against the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Gram-positive bacteria

Staphylococcus aureus (including methicillin-resistant isolates)

(b) (4)

[redacted]

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antibiotic Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Tenth Edition. CLSI document M07-A10. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement. CLSI document M100-S25 Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

7 AGENCY'S PROPOSED CHANGES TO SUBSECTIONS OF THE PACKAGE INSERT

Note: This Reviewer indicates recommended changes to the Microbiology portion of the Package Insert as follows. Deletions are in red and strikethrough font; additions are in blue Font and double underlined.

(b) (4)

[redacted]

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antibiotic Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Tenth Edition. CLSI document M07-A10. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement. CLSI document M100-S25 Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

SIGNATURES:

Kalavati Suvarna, Ph.D. {See appended signature}
Clinical Microbiology Reviewer Signature/Date

Kerry Snow, M.S. M.T. (ASCP). {See appended signature}
Clinical Microbiology Team Leader Signature/Date

CC:
Original NDA
DAIP CSO/Davi, Christopher

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

/s/

KALAVATI C SUVARNA
11/04/2015

KERRY SNOW
11/04/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

<table>
<tr><th colspan="4">Application Information</th></tr>
<tr><td>NDA # 21-883</td><td colspan="2">NDA Supplement #: S- 003</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
X New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Animal Rule Confirmatory Study (SE10)</td></tr>
<tr><td colspan="4">Proprietary Name: Dalvance (dalbavancin hydrochloride) Intravenous Infusion, 500 mg
Established/Proper Name: Dalbavancin
Dosage Form: IV
Strengths: 500 mg</td></tr>
<tr><td colspan="4">Applicant: Durata Therapeutics, International, B.V.
Agent for Applicant (if applicable): N/A</td></tr>
<tr><td colspan="4">Date of Application: July 20, 2015
Date of Receipt: July 20, 2015
Date clock started after UN: N/A</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: January 20, 2015</td><td colspan="2">Action Goal Date (if different): Same</td></tr>
<tr><td colspan="2">Filing Date: September 18, 2015</td><td colspan="2">Date of Filing Meeting: September 2, 2015</td></tr>
<tr><td colspan="4">Chemical Classification (original NDAs only) : N/A
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="4">Proposed indication(s)/Proposed change(s):</td></tr>
<tr><td colspan="3">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☐ 505(b)(1)
☐ 505(b)(2)
X 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard X Priority ☐ Pediatric WR X QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? N/A	Resubmission after refuse to file? N/A
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: QIDP	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): IND 60,613	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	X	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	X		
If yes, explain in comment column.				N/A
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		N/A
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	X	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** X Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	X		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐		X	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐		X	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐		X	
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐		X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	X	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	X	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	N/A
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	N/A
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	N/A

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	X	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	N/A

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	X	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	X	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	X	Requests for deferral have been granted
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	X	DALVANCE is already approved
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	X	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

	X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X	☐		
Is the PI submitted in PLR format?[4]	X	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	X	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	X X	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	X	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	X	☐	☐	
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	X	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	X	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐	X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** May 1, 2015 ***If yes, distribute minutes before filing meeting***	X	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** August 31, 2015 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 2, 2015

BACKGROUND: Filing meeting for S-003, an SE-2 efficacy supplement for a single 1500 mg dose of Dalvance.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	J. Christopher Davi, MS	Y
	CPMS/TL:	Maureen Dillon-Parker	Y
Cross-Discipline Team Leader (CDTL)	Dmitri Iarikov, MD, PhD		Y
Division Director/Deputy	Sumathi Nambiar, MD, MPH		Y
Office Director/Deputy	John Farley, MD, MPH		Y
Clinical	Reviewer:	Rama Kapoor, MD	Y
	TL:	Dmitri Iarikov, MD, PhD	Y
Social Scientist Review (*for OTC products*)	Reviewer:	Not Assigned	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Kalavati Suvarna, PhD	N
	TL:	Kerry Snow, MS	Y
Clinical Pharmacology	Reviewer:	Yang He, PharmD	Y
	TL:	Kimberly Bergman, PharmP	Y
• Genomics	Reviewer:	Not Assigned	
• Pharmacometrics	Reviewer:	Not Asssigned	
Biostatistics	Reviewer:	Christopher Kadoorie, PhD	Y
	TL:	Thamban Valappil, PhD	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Terry Miller, PhD	Y
	TL:	Wendelyn Schmidt, PhD	Y
Statistics (carcinogenicity)	Reviewer:	Chris Kadoorie, PhD	Y
	TL:	Thamban Valappil, PhD	Y
Product Quality (CMC) Review Team:	ATL:	Balajee Shanmugam, PhD	Y
	RBPM:	Dorota Mateka, PhD	Y
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Not Assigned		
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	N/A	
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	N/A	
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Jacqueline Sheppard, PhD	N
	TL:	Vicky Borders-Hemphill, PhD	N
OSE/DRISK (REMS)	Reviewer:	Not Assigned	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Not Assigned	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Not assigned	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Not assigned	
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable X No comments

CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: X NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 X YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 X YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable X YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	N/A ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	X N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Sumathi Nambiar, MD, MPH **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): N/A **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**: None	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: X No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review X Priority Review
ACTION ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
N/A	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
X	If priority review, notify applicant in writing by day 60 (see CST for choices)
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
X	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

JOSEPH C DAVI
01/20/2016

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 21-883/S-003

Application Type: Efficacy Supplement (SE-2)

Name of Drug/Dosage Form: Dalvance (dalbavancin hydrochloride)

Applicant: Durata Therapeutics International, B.V.

Receipt Date: **July 23, 2015**

Goal Date: **January 20, 2016**

1. Regulatory History and Applicant's Main Proposals

Dalvance (NDA 21-883) was approved on May 23, 2014, for the treatment of acute bacterial skin and skin structure infections (ABSSSI). The Sponsor has since submitted an efficacy supplement (SE-2) for a newly proposed dosing regimen.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No deficiencies were identified in the review of this PI.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *None*

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *None*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: *None*

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *None*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *None*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *None*

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Selected Requirements of Prescribing Information

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment: *None*

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *None*

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment: *None*

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment: *None*

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment: *None*

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment: *None*

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *None*

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *None*

YES 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *None*

Indications and Usage in Highlights

N/A 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *None*

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *None*

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *None*

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *None*

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment: *None*

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *None*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment: *None*

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment: *None*

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *None*

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment: *None*

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *None*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *None*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *None*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *None*

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *None*

YES 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment: *None*

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment: *None*

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment: *None*

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment: *None*

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *None*

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *None*

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *None*

N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *None*

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JOSEPH C DAVI
01/05/2016

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE:	December 11, 2015
TO:	J. Christopher Davi, M.S., Senior Regulatory Project Manager Rama Kapoor, M.D., Medical Officer Dmitri Iarikov, M.D., Ph.D., Medical Team Leader Sumathi Nambiar, M.D., M.P.H., Division Director Division of Anti-Infective Products (**DAIP**)
FROM	John Lee, M.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (**OSI**)
THROUGH:	Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation, OSI
SUBJECT:	Evaluation of Clinical Inspections
APPLICATION:	NDA 021883 S-003
APPLICANT:	Durata Therapeutics International, B.V. Ronald Trust, Ph.D., Executive Director Regulatory Affairs, North America
DRUG:	Dalbavancin Hydrochloride (Dalvance®)
NME:	No
INDICATION:	Single-dose regimen as an alternative to two-dose regimen (original NDA approval, May 2014) in treating adults with acute skin and skin structure infections caused by susceptible strains of Gram-positive bacteria.

REVIEW CLASSIFICATION:	Priority Review
APPLICATION SUBMISSION DATE:	July 20, 2015
DARRTS CONSULTATION DATE:	September 2, 2015
INSPECTION SUMMARY GOAL DATE:	December 11, 2015
REGULATORY ACTION GOAL DATE:	January 20, 2015
PDUFA DUE DATE:	January 20, 2015

I. BACKGROUND

Durata Therapeutics International, B.V. (**Durata**) submitted this sNDA 021883 S-003 for Dalvance® (dalbavancin) to include the use of a single-dose regimen as an alternative to the originally approved two-dose regimen in treating adult patients with acute bacterial skin and skin structure infections (**ABSSSI**) caused by susceptible strains of Gram-positive bacteria. The original NDA was approved in May 2014.

Serious skin and contiguous soft tissue infections range from localized cellulitis to necrotizing fasciitis and Fournier's gangrene. In recent years, the changing epidemiology profile of ABSSSI with methicillin-resistant Staphylococcus aureus (**MRSA**) has been a major concern. MRSA is now the most common cause of community-acquired soft tissue infections at major clinical care centers. Dalbavancin is a semisynthetic lipoglycopeptide antibiotic shown to be non-inferior (**NI**) to vancomycin and linezolid in the treatment of ABSSSI, with the major advantages of infrequent (weekly) dosing and its potent activity against Gram-positive bacteria, including MRSA.

Durata sponsored Study DUR001-303 as the pivotal study supporting the use of dalbavancin as a single-dose regimen in treating ABSSSI, as an alternative to the originally approved two-dose regimen. In support of this sNDA review, this study was audited on-site at good clinical practice (**GCP**) inspections of three clinical investigator (**CI**) sites with large contributions to the overall efficacy outcome (subject enrollment and efficacy effect size). This Study DUR001-303 is described briefly below.

Study DUR001-303

A Phase 3b, Double-Blind, Multicenter, Randomized Study to Compare the Efficacy and Safety of Single Dose Dalbavancin to a Two Dose Regimen of Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infections

This double-blind active-controlled study was conducted between April 2014 and March 2015 in 698 adult subjects randomized at 62 CI sites in 11 countries, 24 in the United States (**US**). The primary study objective was to show that a single-dose dalbavancin regimen is not inferior to the labeled two-dose regimen in treating ABSSSI. Subjects were: (1) evaluated (baseline) and randomized in equal ratio to the two treatment groups (regimens), (2) treated with the study medication on Days 1 and 8, (3) evaluated for efficacy on Days 0, 3, 4, 8, 14, and 15, and (4) followed for safety through Day 28. The subject and all study staff were blinded to the treatment assignment, except for the unblinded pharmacist.

Subject Selection

- Adult men or women (age > 18 years) with suspected or confirmed Gram-positive ABSSSI: cutaneous abscess, surgical site infection, traumatic wound infection, and/or cellulitis
- Erythematous lesion with ≥ two additional local signs of ABSSSI: purulent drainage, fluctuance, localized warmth, tenderness, and swelling
- Presence of at least one systemic sign of infection: fever, elevated white blood cell count (**WBC**), or left-shifted WBC (whether elevated or not)

Treatment Groups (Regimens)

- Single-dose regimen: dalbavancin 1500 mg on Day 1 and placebo on Day 8; 1000 mg if creatinine clearance (**CC**) < 30 mL/min; IV infusion over 30 minutes
- Two-dose regimen: dalbavancin 1000 mg on Day 1 and 500 mg on Day 8; 750 mg on Day 1 and 375 mg on Day 8 if CC < 30 mL/min

Major Study Evaluations

- Efficacy: physical examination, infection site assessment, and laboratory testing including microbiology cultures on Days 3/4, 8 (second dose), 14/15 (end of therapy), and 28 (final visit)

- Safety: adverse event (**AE**) monitoring, physical examination, vital signs, and laboratory testing at all study visits through end of study (**EOS**)

Primary Efficacy Assessment

- Measured endpoint: lesion size measurements, longest length (**L**) and perpendicular width (**W**) at baseline and at 48 to 72 hours after treatment initiation
- Derived endpoints: (1) lesion area calculated as L x W at 48 to 72 hours, and (2) clinical response (**CR**) defined as ≥ 20% reduction in lesion size at 48 to 72 hours without rescue therapy
- Analysis, intent-to-treat (**ITT**) population: (1) calculation of CR rate (**CRR**) for each treatment group, and (2) non-inferiority testing to show CRR difference within 10%

Major Sponsor-Reported Outcomes

- Comparable efficacy for the two dalbavancin regimens: early CR was observed in 284 (81%) and 294 (84%) subjects for single and two-dose groups, respectively (lower bound of 95% CI = -8.5, < 10%), with similarly sustained CR through Day 28 (better single-dose treatment compliance).
- Proportions of subjects with treatment-emergent AEs (**TE-AEs)** were similar for the two groups: 78/349 (22%) and 73/346 (21%) for single and two-dose groups, respectively. Most common TE-AEs ≥ 1% in either group were (%, single-dose/two-dose): nausea (3/2), headache (2/1), vomiting (2/1), diarrhea (1/1), dizziness (1/0), cellulitis (0/1), chills (0/1) and localized infection (0/1).
- Changes in laboratory measures were similar for the two groups, including the proportion of subjects with potentially significant elevations in liver function testing (alanine aminotransferase) and/or other laboratory measures used to screen for safety.

II. INSPECTIONS

In auditing Study DUR001-303, the following three CI sites were identified for GCP inspection, based on high subject enrollment and large site-specific efficacy effect size.

- At the three sites (5% of 62, one foreign and two domestic), a total of 154 subjects (22% of 698) were enrolled, each with a CRR of about 95% (mean CRR of about 80% at remaining 59 sites).
- At preliminary sNDA review, no special concerns were identified regarding CI conflict of interest or study conduct, including protocol adherence, protocol violations, safety monitoring, or AE reporting.

	Clinical Investigator Site	Site, Enrollment	Inspection Dates, Outcome
1	Richard C. Keech, M.D. Physician Alliance Research Center 3055 West Orange Avenue, Suite 204 Anaheim, CA	Site 103 49 subjects	Nov 30 – Dec 9, 2015 NAI
2	Robert D. Eyzaguirre, M.D. Alliance Research, Inc. 1932 East Anaheim Street Long Beach, CA	Site 106 52 subjects	Oct 28 – Nov 4, 2015 VAI
3	Vadym Shevchenko, M.D. Cherkasy Regional Hospital 3 Mendeleyeva Street Cherkasy, Ukraine	Site 700 53 subjects	Nov 30 – Dec 4, 2015 NAI

NAI = no action indicated (no significant violations); VAI = voluntary action indicated (minor violations)

1. Richard C. Keech, M.D.

a. What was inspected:

General records: study conduct including institutional review board (**IRB**) and sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, safety (clinical AEs), protocol deviations, and subject discontinuations

b. General observations and comments:

Study DUR001-303, Site 103: 61 subjects were screened, 49 were enrolled (randomized), and 46 completed the study. Case records were reviewed for all subjects, including detailed review for 12 subjects completing study.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following observations were verbally discussed (inspector discretion).

- Subject (b) (6) (randomized to two-dose regimen): Lesion length measured on Day 4 of 12.7 cm was incorrectly reported as 13.7 cm on CRF.

  OSI Comments: This incorrect measurement is relevant to the primary endpoint and analysis, lesion size reduction as measured at 72 hours after the first dose of the study medication (at Day 4). The incorrect measurement favors primary efficacy assessment as less rapid healing for the control (two-dose) regimen, making the test (single-dose) regimen appear more effective relative to the control and favoring sNDA approval. A detailed audit of other primary efficacy endpoint data (including for other subjects) revealed no additional data discrepancies. The incorrect lesion measurement appears to be a single minor isolated data entry error, unlikely to be significant.

- Lyophilized study medication storage at CI site pharmacy: The full range of storage temperature (maximum and minimum temperatures throughout the storage period) apparently was not measured.

  OSI Comments: According to the proposed product label, the lyophilized study medication (prior to reconstitution) is to be stored at 25ºC, with temperature excursions permitted between 15 and 30ºC. At the pharmacy at this CI site, the lyophilized study medication was stored without recording the maximum and the minimum temperatures, but the storage conditions were such that out-of-range temperature excursions were unlikely.

- Subject (b) (6) Serum aspartate and alanine transaminase (**AST** and **ALT**) levels were normal at baseline and elevated up to nearly three-fold the upper limit of normal (**ULN**) at EOS (Day 28 safety evaluation), following study medication dosing on Days 1 and 8. The study monitor advised the CI not to report these AST/ALT elevations as AEs (resolved at repeat testing seventh months later).

- Late filing of financial disclosure (by two months) for one staff member (study coordinator), who participated in evaluation and/or treatment of study subjects

- Duplicate entries on drug accountability log maintained at the CI site pharmacy for the study medication received and dispensed (making audit difficult but verifiable)

All observed deficiencies appear minor, isolated, and unlikely to be significant. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, case report forms (**CRFs**), and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

2. Robert D. Eyzaguirre, M.D

a. What was inspected:

General records: study conduct including IRB and sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, safety (clinical AEs), protocol deviations, and subject discontinuations

b. General observations and comments:

Study DUR001-303, Site 106: 60 subjects were screened, 52 were enrolled (randomized), and 49 completed the study. Case records were reviewed for all subjects, including detailed review for 12 subjects completing study.

A single-item Form FDA 483 was issued for incomplete recordkeeping about handling of the final study medication product, at issue from the pharmacy for IV infusion: specifically, for 16 doses (in as many subjects), the infusion product transport log (pharmacy log) does not show when and who transported the IV infusion product (and not documented on other study records).

OSI Comments:

The study drug was supplied to the CI site as lyophilized powder in single-use vials, to be reconstituted and prepared for IV infusion on-site by an unblinded pharmacist at the scheduled infusion time. The observed recordkeeping deficiency appears to be minor, isolated, and otherwise unlikely to be important to the integrity of the study medication.

Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

3. Vadym Shevchenko, M.D.

a. What was inspected:

General records: study conduct including IRB and sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, safety (clinical AEs), protocol deviations, and subject discontinuations

b. General observations and comments:

Study DUR001-303, Site 700: 54 subjects were screened, 53 were enrolled (randomized), and 52 completed the study. Case records were reviewed for all subjects, including detailed review for 12 subjects completing study.

No significant deficiencies were observed and a Form FDA 483 was not issued. A verbal discussion of minor isolated findings were limited to: (1) for Subject (b) (6) baseline wound culture report showing anaerobic growth was incorrectly reported as aerobic growth on CRF, and (2) for Subject (b) (6) past medical history of congestive heart failure was not reported on CRF. Both observed deficiencies appear minor, isolated, and unlikely to be significant.

Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Durata proposes a single-dose Dalvance® regimen for treating ABSSSI as an alternative to the originally approved two-dose regimen. In support of this sNDA review, the pivotal Study DUR001-303 was audited at GCP inspections of three CI sites (5% of 62) selected for large contribution to the overall study outcome.

A total of 154 subjects were enrolled (22% of 698) at the three sites combined, and the efficacy outcome for the three was higher than for the remaining 59 sites (95% and 80% CRR). Subject case records were reviewed for all enrolled subjects at each site, including detailed review for 36 subjects (23% of 154 audited, 5% of 698 enrolled).

No significant deficiencies were observed at all three CI sites. A Form FDA 483 was issued only at Site 106, for a minor isolated deficiency (about recordkeeping) unlikely to be significant to the study outcome. The study conduct appeared adequate, including the sponsor's oversight of study conduct. All audited data were adequately verifiable and appear reliable as reported in the NDA.

Note: For all three CI sites, the EIR has not been received from the field office and the final inspection outcome remains pending. Upon receipt and review of the EIR, an addendum to this CIS will be forwarded to the review division if the final outcome changes from that reported in this CIS. Close-out correspondence (with CI, copied to review division) otherwise indicates EIR review completion without new significant findings and inspection outcome finalization as reported in this CIS.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

JONG HOON LEE
12/11/2015

JANICE K POHLMAN
12/11/2015

KASSA AYALEW
12/14/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 24, 2015

To: J. Christopher Davi, M.S.
Senior Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Adam George, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, Pharm.D, RAC, CPA
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 021883 Dalvance (dalbavancin) for injection, for intravenous use**

This consult review is in response to DAIP's September 17, 2015 request for OPDP's review of the draft package insert (PI) for NDA 021883 Dalvance (dalbavancin) for injection, for intravenous use. OPDP's comments on the PI are based on the substantially complete version titled "Dalvance1500mg01Sept15FDA.docx" accessed via SharePoint on November 23, 2015. We had one comment for section 6.1 of the PI which is included directly on the attached copy of the labeling, and uploaded to the DAIP SharePoint site on November 23, 2015.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

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/s/

ADAM N GEORGE
11/24/2015

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: August 27, 2015

To: Ni Aye, Khin, M.D., DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Thompson, M.D., Team Leader, GCPAB
CDER OSI PM Track
Name of DSI Primary Reviewer (if known)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Dmitri Iarikov, M.D., Ph.D., Medical Team Leader
Rama Kapoor, M.D., Medical Reviewer
Division of Anti-Infective Products (DAIP)

From: J. Christopher Davi, M.S., Senior Regulatory Project Manager

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21-883/S-003
Applicant: Durata Therapeutics International, B.V.
Applicant Contact: Ronald Trust, PhD
Executive Director, Regulatory Affairs, North America
(203) 871-4610
(973) 452-0505 (cell)
rtrust@duratatx.com

Drug Proprietary Name: Dalvance
Generic Drug Name: dalbavancin hydrochloride
Efficacy Supplement: New dosing regimen (SE-2)
Application Submission Date: July 20, 2015
Review Priority: Priority
Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): Application proposes a new, once weekly dosing regimen for Dalvance (i.e., 1500 mg single dose)

PDUFA Date: January 20, 2016
Action Goal Date: January 20, 2016
Inspection Summary Goal Date: December 11, 2015

II. Protocol/Site Identification

A Phase 3b, Double-Blind, Multicenter, Randomized Study to Compare the Efficacy and Safety of Single Dose Dalbavancin to a Two Dose Regimen of Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infections(ABSSI).

*Study protocol number:**DUR001-303***

The table below lists the DUR001-303 study sites selected for inspection.

Site # (Name,Address, Phone number, email, fax#)	**Protocol ID**	**Number of Subjects [Enrolled/ Screen Failure]**	**Indication/Primary endpoint and other endpoints for verification [*The indication and primary endpoint for this NDA are the same for all sites]***
Site # 103 (US) Physician Alliance Research Center, 3055 W. Orange Avenue Suite 204, Anaheim, CA 92804 714-761-2888	DUR001-303	49/12	Indication: Acute Bacterial Skin and Skin Structure Infections (ABSSI) The primary endpoint: Patients who demonstrated >20% reduction in ABSSSI lesion area at 48 to 72 hours.
Site # 106 (US) Alliance Research, 1932 E Anaheim Street, Long Beach, CA 90813 562-366-2554	DUR001-303	52/8	Same as above
Sites # 700 (UKRAINE) Municipal Institution “Cherkasy Regional Hospital of Cherkasy Regional Council”, Department of Orthopedics and Traumatology 3 Mendeleyeva Str Cherkasy, Ukraine 18009 380505152039	DUR001-303	53/1	Same as above

III. Site Selection/Rationale

Selection Rationale:

i) The selected sites are the three largest sites in the study. These three sites enrolled 154 patients whereas the other 59 sites enrolled 544 patients. Moreover, the three sites reported very high clinical response rates (94%-95%) as compared to other sites (79.4%). Table below provides additional detail on the three selected sites.
Site # 103 and 106 in US and site # 700 in Ukraine, were the largest enrolling sites for the study DUR001-303,

Table: Sites selected for Inspection: Protocol ID: DUR001-303

Site # [Region]	Number of Subjects Enrolled	Responder rates for primary endpoint with 95% CIs:
Site # 103 (US)	49	47/49 ***(95.9%),*** 95% CI: (86.0%, 99.5%)
Site # 106 (US)	52	49/52 ***(94.2%),*** 95% CI: (84.1%, 98.8%)
Sites # 700 (UKRAINE) Municipal Institution "Cherkasy Regional Hospital of Cherkasy Regional Council", Department of Orthopedics and Traumatology 3 Mendeleyeva Str Cherkasy, Ukraine 18009 380505152039	53	50/53 ***(94.3%),*** 95% CI: (84.3%, 98.8%)

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
__X__ High treatment responders (specify): As mentioned above.
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve (e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations)
__X__ Other: Enrollment of a large number of patients and a higher response rate as compared to other study sites.

IV. Tables of Specific Data to be Verified (if applicable)

Please evaluate whether there are discrepancies between case report forms and medical records with regard to the following:

- The proportion of subjects who received prior antibacterial therapy. As per protocol, subjects who received antibacterial therapy within 14 days prior to randomization should be excluded because it may confound the evaluation of study drug efficacy. An exception was allowed for patients receiving a single dose of a short-acting antibacterial drug and no more than 25% of such patients may have been enrolled.
- The proportion of subjects who received additional non-study antibacterial drugs post-randomization.
- The proportion of subjects who have incision and drainage of the index infection before and after enrollment. The proportion of patients with abscesses in the trial should be no more than 30% because surgery alone may resolve skin infection and confound efficacy assessments of study drug.
- Inconsistencies in the skin infection lesion size.

Should you require any additional information, please contact J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702 or Rama Kapoor, MD, Medical Officer, at (240) 494-6267.

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

/s/

JOSEPH C DAVI
09/02/2015

SUMATHI NAMBIAR
09/02/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-883 SUPPL # 003 HFD # 520

Trade Name: DALVANCE

Generic Name: Dalbavancin Hydrochloride, Lyophilized Powder for Injection, 500 mg

Applicant Name: Durata Therapeutics International, B.V.

Approval Date, If Known: January 20, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement? **YES**

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE2 – New dosage regimen

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

d) Has pediatric exclusivity been granted for this Active Moiety?

NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-883 (original NDA approved approved on May 23, 2014)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

NO

If yes, explain: N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

NO

If yes, explain: **N/A**

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical

investigations submitted in the application that are essential to the approval:

In this supplemental Application, approximately 700 adult patients with ABSSSI were studied in a single double-blind multinational Phase 3 trial (DUR001-303). Patients were randomized in a 1:1 ratio to be treated with dalbavancin 1500 mg IV, given as either a single dose of 1500 mg or as 2 doses (1000 mg followed by 500 mg) given 1 week apart. The results from this trial demonstrated that a single 1500 mg dose was non-inferior to the 2-dose regimen, and no new safety risks were identified for either treatment regimen.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in

#2(c), less any that are not "new"):

DUR001-303

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 (DUR001-303) **YES**

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

NO

==========

Name of person completing form: J. Christopher Davi, MS, Sr. RPM, DAIP
Date: January 14, 2016

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH
Title: Director, DAIP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

JOSEPH C DAVI
01/20/2016

SUMATHI NAMBIAR
01/20/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 21-883	NDA Supplement # 003	If NDA, Efficacy Supplement Type: SE2 (newly proposed dosing regimen) *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Dalvance Established/Proper Name: Dalbavancin Dosage Form: Intravenous		Applicant: Durata Therapeutics International, B.V. Agent for Applicant (if applicable): Forest Research Institute, Inc.
RPM: J. Christopher Davi, MS, Senior RPM		Division: Division of Anti-Infective Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: X 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 20, 2016	X AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	N/A
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard X Priority
Chemical classification (new NDAs only): N/A
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	N/A
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes X No
• Indicate what types (if any) of information were issued	None
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	X No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**X** Verified

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP, January 20, 2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	X Included (December 11, 2015)
• Original applicant-proposed labeling	X Included (July 20, 2015)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	N/A
• Original applicant-proposed labeling	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Included (November 2, 2015)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A (Already approved)
❖ Labeling reviews *(indicate dates of reviews)*	RPM: September 2, 2015 OPDP: November 24, 2015
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Included Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	N/A

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC December 2, 2015 If PeRC review not necessary, explain: N/A	
❖ Breakthrough Therapy Designation	N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	N/A
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	N/A
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	N/A
• Pre-sNDA/BLA meeting *(indicate date of mtg)*	June 11, 2015
• EOP2 meeting *(indicate date of mtg)*	No meeting
• Mid-cycle Communication *(indicate date of mtg)*	N/A
• Late-cycle Meeting *(indicate date of mtg)*	N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	None
❖ Advisory Committee Meeting(s)	No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	None
Division Director Summary Review *(indicate date for each review)*	Included – January 20, 2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	Included – January 19, 2016
PMR/PMC Development Templates *(indicate total number)*	None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	CDTL- January 19, 2016
• Clinical review(s) *(indicate date for each review)*	December 4, 2015
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Included (See page 15 of clinical review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Included - December 14, 2015
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	Included – November 4, 2015
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	No separate review
Statistical Review(s) *(indicate date for each review)*	Included – December 15, 2015
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	Included – December 7, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	No separate review
• Supervisory Review(s) *(indicate date for each review)*	No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Included – January 5, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	No carc
❖ ECAC/CAC report/memo of meeting	None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	None
• Primary CMC review/Product Quality Microbiology Assessment	Included – December 7, 2015 Included – October 2, 2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	Microsterility (included; see above)
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	December 8, 2015
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	Acceptable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	**N/A**
• Finalize 505(b)(2) assessment	**N/A**
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	**N/A**
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	None
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	Done
❖ Ensure Pediatric Record is accurate	Done
❖ Send approval email within one business day to CDER-APPROVALS	Done

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/s/

JOSEPH C DAVI
01/20/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-883

DEFERRAL EXTENSION GRANTED

Durata Therapeutics International, B.V.
c/o Durata Therapeutics, Inc.
Attention: Nicole Bradley, PharmD
Director, Regulatory Affairs
Harborside Financial Center, Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Bradley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Dalvance (dalbavancin hydrochloride) Intravenous Infusion, 500 mg, which was approved on May 23, 2014.

We also refer to your request for a deferral extension dated July 20, 2015, for the following Postmarketing Requirement (PMR) that was established under the Pediatric Research Equity Act (PREA):

2145-3: Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from 3 months to 17 years of age with ABSSSI.

Study Completion:	December 2016
Final Report Submission:	June 2017

We have completed our review and we agree with your deferral extension request for this PMR due to your continuing interaction with the Division as it relates to the pediatric drug development program for Dalvance. The Study Completion and Final Report Submission dates for the above listed PMR are revised as follows:

Study Completion:	June 2017
Final Report Submission:	December 2017

You may submit another request for a deferral extension as long as we receive it at least 90 days prior to the original Final Report Submission date and it includes information that substantively differs from what you have previously submitted on this matter.

If you do not submit your required pediatric postmarketing studies by the Final Report Submission date, your reporting status will be shown as delayed and you will be subject to the enforcement mechanism authorized under 505B(d) of the Act, including issuance of a noncompliance letter pursuant to 505B(d)(1). This letter and your response, if any, will be made publicly available on FDA's website at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm343203.htm

sixty days after issuance of the former, with redactions for any trade secrets and confidential commercial information.

Your submission must be made as part of your new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Joseph Toerner, MD, MPH
Deputy Director for Safety
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

JOSEPH G TOERNER
12/16/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 21883 (S-003) **Applicant: Durata Therapeutics, Inc.** **Stamp Date: 7/20/2015**

Drug Name: Dalvance® Powder for Injection Solution **NDA/BLA Type: NDA Supplement-3 (Efficacy)**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		Dalvance is a FDA approved product. The Applicant is seeking a single 1500 mg dose regimen as an alternative to the approved two-dose regimen of 1000 mg on Day 1 and 500 mg on Day 8. There were no nonclinical studies submitted to support the proposed change in dose. (b) (4) There were no nonclinical studies submitted to support the proposed change in dosing.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		See comment to Question #1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		See comment to Question #1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___X_____

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

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

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

(This comment will be sent to the Applicant in the 74-day letter for NDA 21883 S-002 submitted June 26, 2015).

1. The NDA Labeling Supplement (S-002) to NDA 21883 for Dalvance® Powder for Injection was submitted June 26, 2015, and therefore is not subject to the June 30, 2015 deadline that requires all human drugs and biologic products to comply with labeling requirements described in the Pregnancy and Lactation Labeling (PLLR) Final Rule (Dec. 2014). However, NDA Efficacy Supplement (S-003) for NDA 21883 Dalvance® was submitted on 7/20/2015 and therefore is subject to PLLR labeling requirements. In both your NDA Labeling Supplement (S-002) and NDA Efficacy Supplement (S-003) to NDA 21883, the proposed product labeling for Dalvance® is not compliant with requirements for PLLR. To become compliant with PLLR requirements described in the PLLR Final Rule, you will be required to modify your proposed labeling to include subsection (b) (4)

   An internet link to the Final Rule in the Federal Register is included below.

   https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

   Also, the FDA Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug may be helpful to you (internet link below).

   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf

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/s/

TERRY J MILLER
12/03/2015

WENDELYN J SCHMIDT
12/03/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-883/S-003

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Durata Therapeutics International, B.V.
c/o Durata Therapeutics, Inc.
Attention: Nicole Bradley, PharmD
Director, Regulatory Affairs
Harborside Financial Center, Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Bradley:

Please refer to your supplemental New Drug Application (sNDA) dated July 20, 2015, received July 20, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Dalvance (dalbavancin hydrochloride) Intravenous Infusion, 500 mg.

We also refer to your amendments dated August 12, 13, 25 and 27, and September 16, 25 and 30, 2105.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is January 20, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments).We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process.
If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 18, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading

During our preliminary review of your submitted labeling, we have identified the following labeling issue:

Pharmacology/Toxicology:

The proposed product labeling for S-003 (b) (4) To become compliant with requirements described in the Final Rule, you will need to modify your proposed labeling to include subsection (b) (4) .

The Final Rule can be accessed at:

https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

Also, the FDA Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug may be helpful and is available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf

We request that you resubmit labeling (in Microsoft Word format) that addresses this issue by October 23, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see:

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
10/01/2015

Statistical Filing Checklist

NDA Number: 21883 **Applicant:** Durata Therapeutics, Inc. **Stamp Date:** 07/20/15

Drug Name: Dalbavancin **NDA/BLA Type:** 505(b)(1), prior approval efficacy supplement

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			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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/s/

CHRISTOPHER E KADOORIE
09/25/2015

THAMBAN I VALAPPIL
09/27/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21883 **Applicant:** Durata Therapeutics, Inc **Stamp Date:** July 20, 2015

Drug Name: Dalbavancin **NDA/BLA Type:** 505(b)(1); prior approval efficacy supplement

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			ISS (Module 5.3.5.3.iss) has a link to the Clinical Summary of Safety (Module 2.7.4), and separately has pertinent tables, figures and line listings.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			The ISE (Module 5.3.5.3.ise) has a link to the Clinical Summary of Efficacy (Module 2.7.3), and separately has pertinent tables, figures and line listings.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical Overview (Module 2.5), Section 6
12.	Indicate if the Application is a 505(b)(1) or a				505(b)(1)

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	505(b)(2).				
505(b)(2) Applications					
13.	If appropriate, what is the relied upon listed drug(s)?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 DUR001-303 Indication: Acute Bacterial Skin and Skin Structure Infections	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			QT interval study was performed with NDA 21883
23.	Has the applicant presented a safety	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	assessment based on all current worldwide knowledge regarding this product?				
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	Study drugs were administered as a single dose of 1500 mg or two-doses of 100 mg followed by 500 mg (b) (4) days later.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narratives and CRFs are provided
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical 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.

There are no clinical comments for the 74-day letter.

Rama Kapoor, MD — September 10, 2015
Reviewing Medical Officer — Date

Dmitri Iarikov, MD — September 10, 2015
Clinical Team Leader — Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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/s/

RAMA KAPOOR
09/10/2015

DMITRI IARIKOV
09/10/2015

Davi, Christopher

From: Davi, Christopher
Sent: Thursday, September 10, 2015 8:45 PM
To: Ronald Trust (rtrust@duratatx.com)
Cc: Bradley, Nicole (Nicole.Bradley@actavis.com) (Nicole.Bradley@actavis.com)
Subject: NDA 21-883/S-003 Information request for subjects who discontinued study DUR001-303

Hello Ron,

Please see the following information request from the Clinical Team:

Please specify the reason for study discontinuation for subjects who discontinued study DUR001-303 for reasons defined as OTHER. The ADSL dataset identifies 12 such subjects with SDISCREA variable. However, the ADSL dataset does not include an explanation for study discontinuation for these subjects which should be provided under variable SDISREAO.

	USUBJID	SUBJID	AGE	SEX	SAFFL	ITTFL	ACTARM	SDISCR
1		(b) (6)	32	M	Y	Y	1500MG D1 ACTIVE DOSE	OTHER
2			47	F	Y	Y	1000MG D1 500MG D8 ACTIVE DOSE	OTHER
3			51	F	Y	Y	1500MG D1 ACTIVE DOSE	OTHER
4			66	F	Y	Y	1000MG D1 500MG D8 ACTIVE DOSE	OTHER
5			48	M	Y	Y	1000MG D1 500MG D8 ACTIVE DOSE	OTHER
6			58	M	N	N	Not Assigned	OTHER
7			46	M	Y	Y	1000MG D1 500MG D8 ACTIVE DOSE	OTHER
8			48	M	Y	Y	1500MG D1 ACTIVE DOSE	OTHER
9			54	F	N	Y	Not Treated	OTHER
10			23	M	Y	Y	1500MG D1 ACTIVE DOSE	OTHER
11			52	F	Y	Y	1000MG D1 500MG D8 ACTIVE DOSE	OTHER
12			81	F	Y	Y	1000MG D1 500MG D8 ACTIVE DOSE	OTHER

Thanks for your help and let me know if you have any questions.

Regards,

Chris

J. Christopher Davi, MS
Senior Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
christopher.davi@fda.hhs.gov
(301) 796-0702


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/s/

JOSEPH C DAVI
09/10/2015

Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability
NDA 21-883 S003 (DALVANCE TM) by Durata Therapeutics International B.V.
Reviewer: Kalavati Suvarna Ph.D.
Date Review completed: 08/04/2015

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

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	✓		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		
4	On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	✓		
5	Has the applicant submitted draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	✓		
6	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	✓		

Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability
NDA 21-883 S003 (DALVANCE TM) by Durata Therapeutics International B.V.
Reviewer: Kalavati Suvarna Ph.D.
Date Review completed: 08/04/2015

8	Has the applicant submitted the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
9	Has the applicant submitted a clinical microbiology dataset in a format which intends to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	✓		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	✓		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? **IF NO, GIVE REASONS BELOW.**	✓		

Any Additional Clinical Microbiology Comments:
No additional comments.

Reviewing Clinical Microbiologist: Kalavati Suvarna, Ph.D.

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/s/

KALAVATI C SUVARNA
08/14/2015

KERRY SNOW
08/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-883/S-003

ACKNOWLEDGMENT --
PRIOR APPROVAL EFFICACY SUPPLEMENT

Durata Therapeutics International, B.V.
c/o Durata Therapeutics, Inc.
Attention: Ron Trust, PhD, MBA
Executive Director, Regulatory Affairs, North America
322 East Main Street, 3rd Floor
Branford, CT 06405

Dear Dr. Trust:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21-883

SUPPLEMENT NUMBER: 003

PRODUCT NAME: Dalvance (dalbavancin hydrochloride) Intravenous Infusion, 500 mg

DATE OF SUBMISSION: July 20, 2015

DATE OF RECEIPT: July 20, 2015

This supplemental application proposes an alternative dosing regimen (i.e., 1500 mg single dose).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 18, 2015, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be January 20, 2016.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)] in structured product labeling (SPL) format as described at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505/351 of the FDCA/PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at:

http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm.

Additional information regarding Title VIII of FDAAA is available at:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html.

Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 21-883/S-003** submitted on July 20, 2015, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

MAUREEN P DILLON PARKER
07/30/2015