CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MICROBIOLOGY / VIROLOGY REVIEW(S)

Division of Anti-Infective Products

NDA 21—883 SN000 | Clinical Microbiology Review #1
Dalbavancin | Peter Coderre, PhD
Durata Therapeutics | 20 February 2014

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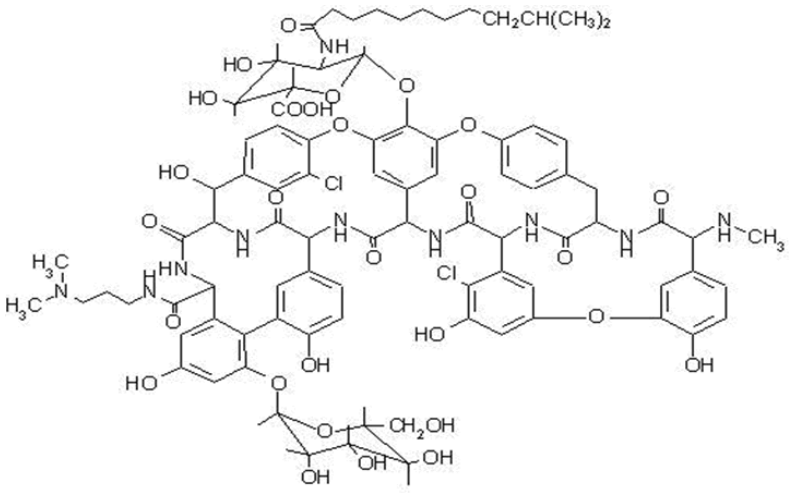
SUBMISSION REVIEWED: NDA 21—883 SN000

INDICATION: 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 isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*).

PRODUCT NAMES:
Proprietary: DALVANCE™
Non-proprietary/USAN: Dalbavancin
Code name: VER001, BI 397, MDL 63, 397, or A-A-1

CHEMICAL NAME: The B0 chemical name is: 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy- 5 6-0-[2-deoxy-2-[(1 0-methyl-1-oxoundecyl) amino] -P-D-glucopyranuronosyl]-3 8- [[[3-(dimethyl amino)propyl]amino]carbonyl]-42-0-P-D-mannopyranosylN15- methylristomycin A aglycone hydrochloride (5:8).

STRUCTURAL FORMULA:
(Major Component B Structure)



Dalbavancin	R_1	R_2	Empirical Formula	Mol. Wt.*
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

DOSAGE FORMULATIONS AND ROUTE OF ADMINISTRATION: Dalbavancin is a powder for concentrate for solution for infusion. Each vial contains 500 mg dalbavancin, and following reconstitution and dilution it is administered intravenously (IV) over a 30-minute period. The proposed dosing regimen is 1000 mg IV on Day 1 and 500 mg IV on Day 8.

PHARMACOLOGICAL CATEGORY: Antimicrobial

DISPENSED: Rx

INITIAL SUBMISSION DATES:

Received by CDER:	25 September 2013
Received by Reviewer:	25 September 2013
Review Completed:	20 February 2014

REMARKS:
Pursuant to Section 505(b) of the Federal Food Drug and Cosmetic Act and 21 C.F.R. § 314.50 and § 314.60, the Applicant submits Durata Serial 1001, under NDA 21-883 for Dalbavancin (DUR001) for injection, a semisynthetic lipoglycopeptide antibiotic. The indication sought is the treatment of adult patients with Acute Bacterial Skin and Skin Structure Infections (abSSSI) caused by susceptible strains of Gram-positive bacteria. This indication is based upon the draft FDA *Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (August 2010). As explained therein, abSSSI has replaced the legacy indication sought in their predecessors' since-withdrawn application, Complicated Skin and Skin Structure Infections (cSSSI).

A Fast Track Status designation was granted to dalbavancin (07 November 2003) for the treatment of cSSSI. The basis of the designation was the potential for treatment of a serious infection caused by a resistant organism (MRSA) and the ability to address an unmet medical need via provision of alternative therapy against MRSA, for which there are limited treatment options. Fast Track status was re-affirmed at the 25 April 2012.

Dalbavancin was granted QIDP status by the Division on 31 October 2012. Section 524A of the FDCA, 21 U.S.C. § 360n-1, requires FDA to classify this application for Priority Review, due to the Division's granting of the above-referenced QIDP designation for dalbavancin.

Background

A dalbavancin NDA (21-883) was previously submitted by Vicuron Pharmaceuticals Inc./Pfizer Inc. and reviewed by the Agency, resulting in three successive Approvable letters from the Agency and three respective Complete Responses from the legacy. During the

Division's review of the third Complete Response, dated 30 May 2008, Pfizer indicated its intent to withdraw the NDA (Pfizer withdrawal letter dated 15 September 2008). Since the time of the NDA's withdrawal in 2008, Durata Therapeutics, Inc., (the Applicant) has assumed whole ownership of Vicuron from Pfizer, including sponsorship of the dalbavancin IND 60,613, and has conducted a total of six clinical studies.

Based on results from the studies listed below, the Applicant has resubmitted NDA 21—883 during the third quarter of 2013, with components and format as agreed at an Operations Type C Meeting that occurred 25 April 2012 (Type C meeting request and briefing document submitted 10 February 2012, SN601; Agency meeting minutes received 21 May 2012).

Phase 3 Studies Conducted by the Sponsor since 2009

The USPI proposal withdrawn by Vicuron/Pfizer in 2008 included efficacy data from Study VER001-9, evaluated in terms of clinical success rates at a Test-of-Cure Visit that occurred two weeks after the end of therapy, with inferential statistics showing statistical non-inferiority for dalbavancin versus linezolid in both a full analysis population and a per protocol population.

- The primary endpoint for this analysis was chosen as two weeks after the end of therapy based on regulatory guidance available at the time Protocol VER001-9 was implemented.
- Since that time, the Agency emphasis has shifted toward a shorter-term primary endpoint, namely 48-72 hours after the first dose of study medication.

Thus, two new Phase 3 studies, Studies DUR001-301 and DUR001-302, have been conducted that are considered pivotal trials for resubmission of the dalbavancin NDA. Both of these studies were designed in alignment with updated regulatory requirements for the indication of abSSSI, and each was the subject of an Agreement with the Division based on the Special Protocol Assessment procedure. It is the Sponsor's position that the results of Studies DUR001-301 and DUR001-302, in which the primary endpoint occurred 48-72 hours after the first dose of study medication, complement and extend the results observed for Study VER001-9 at its 2-week primary endpoint, and that together the results of all three of these Phase 3 studies provide a valuable representation of the efficacy profile to be expected for dalbavancin in real-world abSSSI patients.

Studies DUR001 -301 and DUR001-302 were randomized, double-blind, double-dummy studies of similar design that evaluated the efficacy and safety of dalbavancin in the treatment of adult patients with abSSSI. Patients were randomized to receive active treatment, either with the standard IV dalbavancin regimen on Day 1 and Day 8, or with comparator treatment using IV vancomycin (with possible switch to oral linezolid after at least three days of intravenous treatment) for 10-14 days. Matching IV and/or oral placebo was provided to maintain the blinded trial design. Altogether, a total of 1312 patients were randomized in these two Phase 3 studies, including 659 patients randomized to dalbavancin and 653 patients randomized to comparator.

RECOMMENDATIONS AND CONCLUSION:

From the Microbiology standpoint, **NDA 21—883 is approvable** contingent upon the acceptance of the changes to the Microbiology Section of the Package Insert. This Reviewer makes no additional recommendations at this time.

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MICROBIOLOGY SUBSECTION 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.

12.4 Microbiology

(b) (4) *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.

(b) (4) *Mechanism of Resistance~~:~~*
The development of bacterial (b) (4) isolates resistant to dalbavancin has not been observed, either *in vitro* in studies using serial passage, or in animal infection experiments. (b) (4)

Interaction with Other (b) (4) *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.

(b) (4)

(b) (4) Dalbavancin has been shown to be active against (b) (4) the following microorganisms, both *in vitro* and in clinical infections (b) (4) ~~*[see*~~ INDICATIONS AND USAGE (b) (4) ~~*(1)].*~~

(b) (4) <u>Gram-positive bacteria</u>
*Staphylococcus aureus (*including methicillin-resistant isolates)
Streptococcus pyogenes
Streptococcus agalactiae
~~*Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*)~~

Reviewer's comments: Due to the limited number of clinical isolates (nine), the lack of clinical experience prevents the inclusion of *Streptococcus anginosus* group in the first

list. In addition, the lack of MICs from speciated isolates in the surveillance studies prevents the inclusion of *Streptococcus anginosus* group in the second list.

(b) (4) The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of organisms in the following (b) (4) bacteria (b) (4) exhibit (b) (4) an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the (b) (4) (b) (4) However, the safety and (b) (4) efficacy of dalbavancin in treating clinical infections due to these (b) (4) bacteria ~~have~~ (b) (4) not been established in adequate well-controlled clinical trials.

(b) (4) Gram-positive bacteria
(b) (4)

Enterococcus faecalis (vancomycin-susceptible (b) (4) isolates only)
Enterococcus faecium (vancomycin-susceptible (b) (4) isolates only)

Reviewer's comments: For organisms to be included in the second list, they must be identified to the species level. While the Applicant provided large amounts of MIC susceptibility data for beta-hemolytic streptococci, these data were not differentiated for speciated organisms; thus beta-hemolytic streptococci cannot be included in the second list.

The Applicant provided large amounts of MIC susceptibility data for coagulase negative staphylococci (CoNS); however, these data may include several different species of Staphylococci in addition to *Staphylococcus epidermidis*. As the Applicant did not provide MIC data from 100 isolates of *Staphylococcus epidermidis*, this organism cannot be included in the second list.

Susceptibility Test Methods

(b) (4)

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 product for treatment.

Dilution techniques~~:~~
Quantitative methods are used to determine minimum inhibitory concentrations (MICs) (b) (4) These MICs provide estimates of the susceptibility of (b) (4) bacteria (b) (4) to (b) (4) antimicrobial compounds. The MICs should be determined using a (b) (4)

(b) (4) standardized test method~~s~~1,2 (b) (4) 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 (b) (4) MIC values (b) (4) should be interpreted according to ~~the~~ criteria provided in Table 6.

(b) (4) -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 (b) (4) 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)	≤ 0.12	--	--	--	--	--
Streptococcus pyogenes and *Streptococcus agalactiae*	≤ 0.12	--	--	--	--	--

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.

(b) (4)

Reviewer's comments: The combination of surveillance, clinical trial, animal efficacy models and PK/PD modeling do not support the Applicant's proposed MIC susceptibility interpretive criterion of 0.25 µg/mL. We recommend a MIC susceptibility interpretive criterion of 0.12 µg/mL for all three organisms based on the calculation of a weighted average of all four criteria used to determine the susceptibility breakpoint. For details of the breakpoint determination, see the section on Breakpoint Discussion in this review.

Based on the lack of surveillance and clinical trial data, the *S. anginosus* group cannot be included in either the first or second list in the Microbiology section of the package insert. Consequently, a susceptibility breakpoint cannot be assigned for the *S. anginosus* group.

A report of "Susceptible" indicates that the antibacterial agent is likely to inhibit growth of the pathogen if the antibacterial (b) (4) compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. (b) (4)

(b) (4)

Quality Control:
Standardized susceptibility test procedures require the use of (b) (4) laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents using 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 (b) (4)

Table (b) (4) Acceptable Quality Control Ranges for Dalbavancin

(b) (4) Strain	MIC Range (mcg/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

[a] This organism may be used for validation of susceptibility test results when testing *Streptococcus* (b) (4) other than *S. pneumoniae*.
ATCC ®= American Type Culture Collection

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antibiotic Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Ninth Edition*. CLSI document M07-A9. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, (b) (4) 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement*. CLSI document M100-S23. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, (b) (4) 2013.

EXECUTIVE SUMMARY

Bacterial infections of the skin and underlying soft tissues are among the most common presentations in patients visiting emergency room clinics and hospitals. Most such infections are caused by *Staphylococcus aureus* or *Streptococcus pyogenes.* While *S. pyogenes* remains susceptible to penicillins, the emergence of resistance to all beta- lactam antibiotics in *S. aureus* raises a threat to public health. Until the approval of antibiotics such as linezolid, tigecycline and daptomycin, glycopeptides such as vancomycin and teicoplanin were the only available options for treating most serious infections due to methicillin resistant strains. While the newer antibiotics have excellent activity against Gram-positive pathogens, they also have specific limitations.

Dalbavancin is a second generation, semi-synthetic, lipoglycopeptide antibiotic, structurally related to teicoplanin, that presents improved features with respect to the classical glycopeptides, vancomycin and teicoplanin, including both significantly improved *in vitro* potency and a pharmacokinetic profile that allows weekly dosing.

The Applicant submits an application seeking the approval of (b) (4)™ (dalbavancin) for the treatment of adult patients with acute bacterial skin and skin structure infections (abSSSI) caused by the susceptible strains of the following Gram-positive bacteria: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*).

The mechanism of action of dalbavancin involves the interruption of cell wall synthesis by binding to the terminal D-ala-D-ala of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits. This results in bacterial cell death.

Resistance to dalbavancin among Gram-positive bacteria appears to be limited to certain intrinsically glycopeptide-resistant species and to bacteria expressing the VanA phenotype of acquired resistance. Dalbavancin, like teicoplanin, is active against the intrinsically vancomycin-resistant enterococcal species expressing the VanC phenotype and against VanB strains with acquired resistance, but is not active against other intrinsically glycopeptide-resistant Gram-positive species such as pediococci, leuconostocs and some species of lactobacilli.

Dalbavancin is active against a spectrum of important Gram-positive pathogenic bacteria, generally with more potency than other glycopeptides and most other classes of comparators. Of particular relevance is the activity of dalbavancin against all species of staphylococci, including methicillin-resistant multi-drug resistant *S. aureus,* as well as streptococci including *S.*

pyogenes and *S. agalactiae*. Dalbavancin has *in vitro* activity against teicoplanin-resistant, coagulase-negative staphylococci, vancomycin susceptible enterococci, and vancomycin-resistant enterococci not carrying the VanA resistance cassette (*eg*, VanB and VanC). Activity of dalbavancin has also been demonstrated against Gram-positive anaerobes and most Gram-positive non-acid-fast bacilli (including *Bacillus anthracis).*

Prospective worldwide surveillance of the *in vitro* potency of dalbavancin, in comparison with other antimicrobial agents, was begun in 2002 and has continued through 2012, with several thousand Gram-positive clinical isolates (principally staphylococci, streptococci and enterococci) tested in most years. The emphasis has been on species that are relevant to the proposed indication, acute bacterial skin and skin structure infection (abSSSI), including methicillin-resistant *Staphylococcus aureus* (MRSA) and multiply resistant isolates. Additionally, the potency of dalbavancin against collections of specific organism categories was examined in a number of studies. The MIC90s from US and European isolates of staphylococci, streptococci and enterococci were nearly identical.

The activity of dalbavancin was compared against a panel of antibiotics used to treat Gram positive infections. Dalbavancin had the lowest MIC90 of any antibiotic tested against *S. aureus*. Dalbavancin had greater potency against beta hemolytic streptococci than the comparators, with the exception of penicillin, which had a similar MIC range and MIC90. Dalbavancin had greater potency against viridans streptococci than any of the comparators with a MIC90 value of 0.06 μg/mL.

Although in general glycopeptide antibiotics do not have activity against Gram-negative bacteria, dalbavancin only has *in vitro* activity against certain fastidious Gram-negative bacteria.

No antagonism has been observed *in vitro* between dalbavancin and other agents commonly used to treat Gram-positive infections. Potentially useful synergy with oxacillin has been reported against some MRSA and VISA strains and with ampicillin against VanA enterococci. Interactions of vancomycin and teicoplanin with other agents have been extensively investigated, in particular against resistant organisms such as MRSA and VRE, where combination therapy may have advantages. *In vitro* synergy is often observed between glycopeptides and β-lactams or aminoglycosides. Importantly, antagonistic interactions have rarely been observed for the glycopeptide class of antibiotics.

Dalbavancin is bactericidal *in vitro* for staphylococci and streptococci at free drug concentrations that are sustained in patients treated with the proposed regimens. The bactericidal activity of dalbavancin *in vitro* is time-dependent, as is the case for vancomycin and teicoplanin. While the *in vitro* activity of dalbavancin is affected by the addition of serum, its inhibitory and bactericidal activities are evident at concentrations lower than the concentrations of free drug that are maintained over the entire dosage interval with the

proposed regimen; due to the $t_{1/2}$ of dalbavancin in humans, bactericidal concentrations are present for up to a week after administration of each dose.
The time-dependent bactericidal activity of dalbavancin *in vitro* suggested that time above the MIC may be the important PD parameter of efficacy for dalbavancin. In the neutropenic mouse thigh infection model, AUC of unbound drug/MIC correlated best with the efficacy of dalbavancin against *S. aureus* and *S. pneumoniae*. In this and other models, widely spaced, large doses were very effective, supporting the weekly human dosage regimen.

The Applicant conducted a series of studies of animal infections with Staphylococci. These animal models include mice, rats and rabbit as well as immunocompetent and neutropenic models. Bacterial strains utilized in these studies were *S. epidermidis* and *S. aureus* (both methicillin susceptible and methicillin resistant). These studies were done in a variety of body sites in animals. The range of highest, efficacious MIC ran from 0.06 mcg/ml in neutropenic mice in the lung due to MSSA and subcutaneous implants in rabbits infected with MSSA to 4 mcg/ml in rabbits with endocarditis infected with MRSA and VISA. (b) (4)

The Applicant conducted a series of studies of animal infections with Streptococci. These animal models include both mice and rats as well as immunocompetent and neutropenic models. Bacterial strains utilized in these studies were *S. pyogenes* and *S. pneumoniae* (both penicillin susceptible and penicillin resistant). These studies were done in a variety of body sites in animals. The range of highest, efficacious MIC ran from 0.015 mcg/ml (in immunocompetent and neutropenic rats with lobar pneumonia due to PSSP and PSRP) to 0.25 mcg/ml (in immunocompetent rats with pneumonia infected with PRSP). (b) (4)

Recently, these PK/PD target attainment simulations have been updated using more recent MIC surveillance data and an enhanced population PK model based on study VER001-9. These PK exposures were then used in a PK/PD analysis to examine relationships between dalbavancin PK exposure and outcome at EOT. Monte Carlo simulation analyses were also conducted to assess PK/PD target attainment using both animal- and clinically-derived PK/PD targets for efficacy.

The Applicant believes these analyses provide additional support for an *in vitro* susceptibility criterion of ≤ 0.25 µg/mL. The Applicant also believes the available data from this family of analyses suggest that the same criterion would be applicable to β-hemolytic and viridans streptococci. From the Microbiology standpoint, it appears the target attainment simulations support a susceptibility breakpoint of ≤ 0.25 µg/mL for either staphylococci or streptococci.

The reference method used to determine the *in vitro* activity of dalbavancin is the broth microdilution method of the Clinical and Laboratory Standards Institute (CLSI) (CLSI 2012a, CLSI 2013), which has been used in the majority of studies, including the characterization of clinical trial isolates. 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 Applicant conducted studies of the effects of variations in test conditions on the *in vitro* activity of dalbavancin. Initial testing of individual variables that might affect results was based on standard CLSI broth microdilution and agar dilution procedures (CLSI 2012a). Although standards of medium, inoculum size, *etc*. are stipulated, it is recognized that deviations from these methods can occur. Both CLSI and EUCAST methods include variables such as: inoculum size; incubation time and conditions; growth medium pH, composition and cation concentrations.

Among the variables usually explored, only the addition of serum has a negative effect on the *in vitro* activity of dalbavancin, although in absolute terms MIC values and bactericidal concentrations of dalbavancin in the presence of 50% human serum are well below levels that are maintained in human plasma with the proposed dosage regimens.

However, it became clear that the major factor influencing dalbavancin broth microdilution MICs is the manner in which panels are prepared. This is related to solubility and the tendency of dalbavancin to adhere to plastic materials. More recently it has been shown that dalbavancin agar dilution MICs are higher than those determined by broth microdilution; this has implications for the accurate assessment of the susceptibility to dalbavancin of those organisms, such as anaerobes, that are normally tested on agar.

In the course of the Quality Control (QC) studies, *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).

Table A summarizes the QC ranges obtained during the clinical trials and in performing the surveys of non-clinical trial isolates. In this summary report, it shows that all values were within CLSI (NCCLS) QC range established for dalbavancin.

Table A. Quality control ranges obtained in the *in vitro* susceptibility testing of isolates recovered in clinical trials and worldwide surveys

QC Strain	MIC mcg/mL		
	Mode	Range	% in range
E. faecalis ATCC® 29212	0.06	0.03-0.06	100%
S. aureus ATCC ®29213	0.03	0.03-0.-06	100%
S. pneumoniae ATCC® 49619	0.016	≤0.008-0.03	100%

Based on the report provided by the Applicant, it appears that the QC data for dalbavancin obtained during the clinical trials and surveys using the dry-format microtiter trays were in range and the results were acceptable.

The efficacy of dalbavancin for the targeted treatment indication of abSSSI and cSSTI was evaluated in three pivotal studies (DUR001-301, DUR001-302, and VER001-9). Each of these were randomized, double-blind (third party unblinded), multi-center studies. Patients with infections consistent with abSSSI or cSSTI, both defined as infections involving deeper soft tissue or requiring significant surgical intervention, were eligible for DUR001-301 and Study DUR001-302 or VER001-9, respectively.

Various responses are compared for the pooled abSSSI data set in Table B. These include early response parameters and clinical status of success at EOT, which were specific to the DISCOVER program, for DUR001-301 + DUR001-302. Investigator assessment of response at EOT, which was an end point in all three studies, is presented for the pooled DISCOVER studies and also for these data pooled with the VER001-9 reanalysis subset.

At the early time point (48-72 hours) the success rate in DUR001-301 + DUR001-302, as measured by a >20% reduction in lesion size, an objective measurement, was generally higher than for clinical response, particularly in the dalbavancin treatment arm. At EOT, response rates were >90% for most pathogens in both treatment arms. Due to the smaller sample sizes, the response rates for *S. agalactiae*, *S. dysgalactiae* and *S. anginosus* group streptococci were more variable.

Table B. Successful Clinical Outcomes by Key Target Pathogen in Patients with Monomicrobial Infection

	48-72 Hours [1] (microITT)				End of Treatment [1] (ME)				End of Treatment [2] (ME)	
	Early Response		>20% Lesion Reduction		Clinical Status (ME)		Investigator Assessment		Investigator Assessment	
Baseline Pathogen	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator[3]
S. aureus (All)	172/208 (82.7)	169/196 (86.2)	196/208 (94 2)	182/196 (92.9)	173/191 (90.6)	166/177 (93.8)	176/191 (92 1)	166/167 (93.8)	344/377 (91.2)	261/283 (92.2)
MRSA	66/82 (80.5)	47/57 (82.5)	75/82 (91.5)	50/57 (87.7)	66/74 (89.2)	48/50 (96.0)	67/74 (90.5)	48/50 (96.0)	167/184 (90.8)	99/109 (90.8)
MSSA	106/126 (84.1)	121/138 (87.7)	121/126 (96.0)	131/138 (94.9)	107/117 (91.5)	117/126 (92.9)	109/117 (93.2)	117/126 (92.9)	177/193 (91.7)	161/173 (93.1)
S.pyogenes	16/19 (84.2)	8/14 (57.1)	17/19 (89.5)	10/14 (71.4)	18/19 (94.7)	11/13 (84.6)	18/19 (94.7)	12/13 (92 3)	24/27 (88.9)	15/16 (93.8)
S.agalactiae	4/7 (57.1)	2/3 (66.7)	5/7 (71.4)	2/3 (66.7)	6/7 (85.7)	1/2 (50.0)	6/7 (85.7)	1/2 (50.0)	11/12 (91.7)	4/6 (66.7)
S.dysgalactiae	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	4/4 (100)	2/2 (100)
S.anginosus group	6/9 (66.7)	9/9 (100)	8/9 (88.9)	9/9 (100)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)
S.anginosus	1/2 (50.0)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
S.constellatus	3/5 (60.0)	6/6 (100)	4/5 (80.0)	6/6 (100)	5/5 (100)	5/6 (83.3)	5/5 (100)	5/6 (83.3)	5/5 (100)	5/6 (83.3)
S.intermedius	2/2 (100)	1/1 (100)	2/2 (100)	1/1 (100)	1/2 (50.0)	1/1 (100)	1/2 (50)	1/1 (100)	1/2 (50)	1/1 (100)

Responses are success/total (%).
1 Includes patients from DUR001-301 and DUR001-302
2 Includes patients from DUR001-301, DUR001-302 and reanalysis subset of VER001-9.
3 Vancomycin/Linezolid in studies DUR001-302 and DUR001-302; Linezolid in VER001-9.
Source: Table 63, Microbiology Summary, this submission.

The clinical efficacy of dalbavancin was also not related to MICs for baseline isolates from any species. This is illustrated by the clinical status of success at EOT and the investigator's assessment of clinical outcome at EOT as a function of baseline MIC in patients with a single baseline pathogen.

Based upon population PK and target attainment considerations, the Applicant proposes the susceptibility breakpoints for dalbavancin as ≤ 0.25 μg/mL for *S. aureus, S. pyogenes, S. agalactiae* and *S. anginosus* group. From the clinical microbiology perspective, the data provided by the Applicant do not provide sufficient clinical experience to support the Applicant's proposed breakpoint for susceptibility interpretive criteria of ≤ 0.25 μg/mL the target pathogens in the proposed Indication and Usage for dalbavancin. In addition, the low number of clinical data for the *S. anginosus* group prevent inclusion in the indication section

and the first list of the Microbiology subsection of the Package Insert. Consequently, a breakpoint is not calculated for the *S. anginosus* group.

In the table below, the breakpoint parameters derived from the various data for each pathogen are listed:

Table C. Breakpoint Parameters for Each Pathogen

Breakpoint Parameter	*S. aureus*	*S. pyogenes*	*S. agalactiae*
Surveillance MIC90	0.06	0.03	0.06
Clinical isolate MIC90 or mode	0.06	0.015	0.03
PK/PD Monte Carlo simulations	0.25	0.25	0.25
Mouse thigh model MIC	0.12	0.03	0.03

If each parameter is weighted equally, the following MIC interpretive criteria were calculated for each pathogen:

Table D. Weighted Average Breakpoints for Each Pathogen

Calclulation	Breakpoint (mcg/ml)	Pathogen
0.06(.25)+0.06(.25)+0.25(0.25)+0.12(.25)=	0.123	*S. aureus*
0.03(.25)+0.015(.25)+0.25(.25)+0.03(.25)=	0.081	*S. pyogenes*
0.06(.25)+0.03(.25)+0.25(.25)+0.03(.25)=	0.093	*S. agalactiae*

While none of these breakpoints are an exact MIC dilution, when approximated, each of these breakpoints is 0.12 μg/mL.

Thus, based on the data from the dalbavancin surveillance MICs, the clinical isolate MICs, the Monte Carlo simulations and the animal efficacy data, the Agency proposes the following interpretive criteria:

Table E. MIC Susceptibility Test Result Interpretive Criteria for Dalbavancin

Pathogen	MIC (mcg/mL)			Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.12	--	--	--	--	--
Streptococcus pyogenes and *Streptococcus agalactiae*	≤ 0.12	--	--	--	--	--

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If an isolate yields an MIC result other than susceptible it should be retested being sure that the test is performed correctly. If the results are other than susceptible on re-test, the isolate should be submitted to a reference laboratory for testing.

There was no resistance to dalbavancin among any clinical trial isolates (either at baseline or emerging during therapy) or in worldwide surveys of clinical trial isolates, and no resistance has been generated in laboratory experiments. Thus, only a susceptibility breakpoint has been designated. In addition, no disk diffusion interpretive criteria are assigned due to the lack of a valid disk diffusion methodology.

Finally, the Agency agrees with the Applicant's proposed *in vitro* susceptibility test quality control parameters as indicated below:

Table F. Acceptable MIC (µg/mL) Quality Control Ranges for Dalbavancin

QC Strain	MIC Range (mcg/mL)
Staphylococcus aureus ATCC ®29213	0.03-0.12
Streptococcus pneumoniae ATCC ® 49619a	0.008-0.03
Enterococcus faecalis ATCC ®29212	0.03-0.12

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

INTRODUCTION

Bacterial infections of the skin and underlying soft tissues are among the most common presentations in patients visiting emergency room clinics and hospitals. Most such infections are caused by *Staphylococcus aureus* or *Streptococcus pyogenes.* While *S. pyogenes* remains susceptible to penicillins, the emergence of resistance to all beta- lactam antibiotics in *S. aureus* raises a tremendous threat to public health. Until the approval of antibiotics such as linezolid, tigecycline and daptomycin, glycopeptides such as vancomycin and teicoplanin were the only available options for treating most serious infections due to methicillin resistant strains. While the newer antibiotics have excellent activity against Gram-positive pathogens, they also have specific limitations:

- Linezolid is contraindicated in patients who are using selective serotonin reuptake inhibitors and is associated with bone marrow suppression;
- Approved product documentation for tigecycline was recently updated to include information regarding increased mortality associated with its use;
- Daptomycin is associated with concerns regarding rhabdomyolysis and the emergence of resistance on therapy; and
- Ceftaroline requires twice daily IV administration over many days.

Dalbavancin is a second generation, semi-synthetic, lipoglycopeptide antibiotic, structurally related to teicoplanin, that presents improved features with respect to classical glycopeptides, vancomycin and teicoplanin, including both significantly improved *in vitro* potency and a PK profile that allows weekly dosing.

The Applicant submits an application seeking the approval of (b) (4) ™ for the treatment of adult patients with acute bacterial skin and skin structure infections (abSSSI) caused by the susceptible strains of the following Gram-positive bacteria:

- *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates),
- *Streptococcus pyogenes*,
- *Streptococcus agalactiae* and
- *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*).

PRECLINICAL EFFICACY—*IN VITRO*

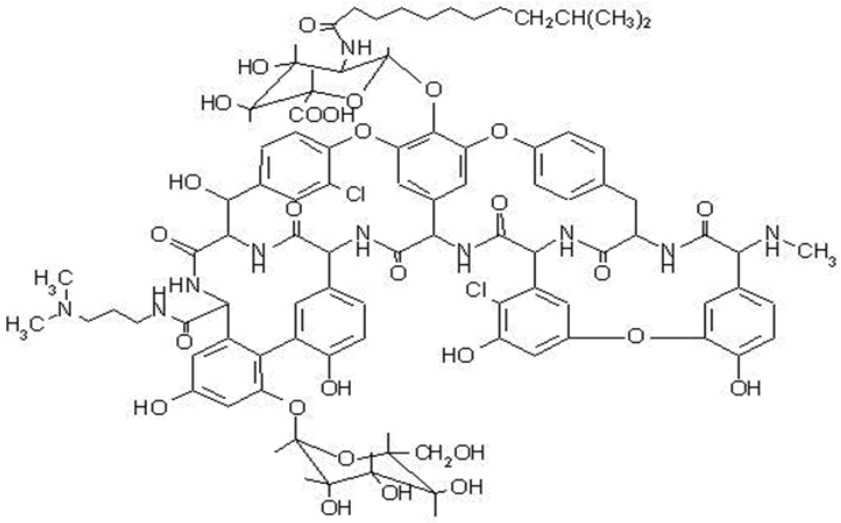
Reviewer's Note: This application was previously reviewed and recommended for approval by the original Microbiology reviewer, Connie Mahon. For detailed information, the reader is referred to the original review by Connie Mahon. What follows is the summarized information contained in that review and the current submission.

MECHANISM OF ACTION

Dalbavancin (also known as BI397, VER001 and V-glycopeptide) is a semi-synthetic glycopeptide antibiotic being developed as an intravenous (IV) treatment for acute bacterial skin and skin structure infections (abSSSI). The majority of these infections are caused by Gram-positive bacteria, including strains resistant to currently available antimicrobial agents.

Dalbavancin (Figure 1) is a derivative of the natural glycopeptide A-40926, which is produced by a *Nonomuraea* sp. A characteristic of A-40926 and other teicoplanin-like glycopeptides is a long fatty acid chain attached to [redacted] (b) (4) the presence of which correlates with an extended half-life ($t_{1/2}$) *in vivo*, as compared with vancomycin-like glycopeptides. Glycopeptides that have a fatty acid chain have been termed lipoglycopeptides. [redacted] (b) (4)

Figure 1. Chemical Structure of Dalbavancin (Major Component B0)



Source: Figure 1, Microbiology section, this submission.

Glycopeptides inhibit cell wall crosslinking (transglycosylation and transpeptidation reactions) by binding to the D-ala-D-ala dipeptide of nascent peptidoglycan. The inhibitory action of β-

lactam antibiotics is due to their binding to the active site of these enzymes; in contrast, glycopeptide antibiotics bind to the substrate, D-ala-D-ala. The same biosynthetic processes occur in Gram-negative bacteria; however, glycopeptides are generally inactive against these organisms because they do not penetrate the outer membrane.

No other therapeutically used antibiotic class has this specific mechanism of action, and there is no cross resistance between glycopeptides (including dalbavancin) and other antibiotic classes. Dalbavancin has greater *in vitro* potency and a longer $t_{1/2}$ than currently available glycopeptides.

Dalbavancin, like other glycopeptide antibiotics, interferes with cell wall formation by binding to the D-alanyl-D-alanine (D-ala-D-ala) terminus of the stem pentapeptide of nascent peptidoglycan, preventing cross-linking. This appears to be the sole mechanism of action of dalbavancin.

Other semi-synthetic glycopeptides (including oritavancin and telavancin) have been described that differ from dalbavancin, vancomycin and teicoplanin in having rapid, concentration dependent bactericidal activity and/or being active *in vitro* against all or most VanA strains of *Enterococcus* spp. (Cooper 1996, Debabov 2002, Debabov 2003). Both of these compounds have multiple mechanisms of action. Oritavancin was shown to directly inhibit the transglycosylase enzyme of *Escherichia coli* in a cell-free assay, in contrast to vancomycin (Ge 1999, Chen 2003), whereas telavancin has been shown to permeabilize the bacterial cell membrane (Higgins 2005).

MECHANISMS OF RESISTANCE

With the exception of the very rare vancomycin-resistant *S. aureus* (VRSA) strains, no staphylococci or streptococci resistant to dalbavancin have been detected among thousands of isolates from surveillance studies and dalbavancin clinical trials. Dalbavancin is active against some organisms that are resistant to vancomycin or teicoplanin. A number of VISA strains have appeared globally over the past several years. These strains are more susceptible to dalbavancin than to vancomycin. However, most of the rarely encountered VRSA strains are likely not susceptible to dalbavancin, as they carry the *vanA* determinants.

As discussed in the section on mechanism of action, the activity of dalbavancin requires bacteria have a cell wall and an appropriate target dipeptide (usually D-ala-D-ala). Bacteria that normally have no cell walls (mollicutes) are refractory to the effects of glycopeptides, as well as to other cell wall inhibitors such as β-lactams. Most Gram-negative bacteria are impermeable to glycopeptides and thus resistant to glycopeptides.

Glycopeptide Resistance in Enterococci

Enterococci that have acquired the ability to modify the stem peptide in nascent peptidoglycan are resistant to vancomycin when they are expressing the altered cell wall precursors. In general, the normal D-ala-D-ala is produced unless there is induction of the alternate pathway. VanA enterococci are induced by glycopeptides to produce D-alanyl-D-lactate (D-ala-D-lac) and are therefore resistant to these agents. Glycopeptide resistance in enterococci is the result of the concerted action of a cluster of genes whose activity leads to the production of alternative peptidoglycan precursors that have reduced affinity for vancomycin (Arthur 1993a, Gold 2001, Arthur 1996, Bugg 1991). There are a variety of enterococcal glycopeptide resistance determinants; they will not be discussed in detail here as the Applicant does not seek a claim against enterococci. The transfer of resistance among enterococci (and possibly to other clinically relevant pathogens) is mediated by transposons that are able to form co-integrate plasmids. Dalbavancin is active against VanB and VanC isolates. VanD, VanE and VanG isolates, which are more rarely encountered, have not been tested. The dalbavancin MIC range for phenotypically VanA (teicoplanin-resistant) enterococci is quite broad, with dalbavancin showing greater activity against some isolates.

Glycopeptide Resistance in Staphylococci

Resistance to vancomycin is seen in CoNS, but not frequently. However, reduced susceptibility or resistance to teicoplanin is regularly observed among CoNS (Cercenado 1996). In general, these strains have greater susceptibility to dalbavancin.

Less frequently encountered is reduced susceptibility to vancomycin in *S. aureus* (VISA strains). The MIC90 of dalbavancin against a set of VISA strains was 1 µg/mL (Report VER001-MI-004). In another study, dalbavancin MICs for 36 hVISA strains were 0.03-0.12 µg/mL (Campanile 2010). Although most strains of VRSA have not been tested, those with high-level resistance to teicoplanin are expected to also be resistant to dalbavancin.

The first *S. aureus* strain displaying resistance to high levels of vancomycin (MIC >32 µg/mL) was isolated in 2002 from a patient in Michigan (CDC 2002a). Of 11 strains isolated to date in the US, most of them have been from Michigan (Périchon 2012, Périchon 2009). Very few VRSA strains have been reported from other countries. Most but not all of these strains are also highly resistant to teicoplanin. Where investigated, resistance in VRSA is mediated by *vanA* genes originating in enterococci.

Vancomycin-Intermediate *Staphylococcus aureus* (VISA)

S. aureus isolates with reduced susceptibility to vancomycin were isolated in Japan in 1996 and in the US in 1997 (Hiramatsu 1997, CDC 1997a, CDC 1997b), and continue to be found, infrequently in a variety of settings. Vancomycin MICs ranged from 8–16 µg/mL for these isolates, giving them the characterization Vancomycin-Intermediate *S. aureus* or VISA. Unlike VRSA, VISA strains do not harbor the *vanA* gene or other similar genes or gene clusters. Rather,

they are characterized by unusually thick cell walls (Cui 2000). Although the peptidoglycan composition and termini do not appear to be altered in these isolates, the thickened cell walls contain many more D-ala-D-ala termini than usual, and this multiplicity of glycopeptide targets is thought to be one factor responsible for reduced susceptibility.

VISA populations tend initially to be heterogeneous (hVISA), containing fully susceptible organisms in the presence of sub-populations with higher vancomycin MICs (although below the resistance breakpoint). It has been suggested that exposure to low levels of vancomycin leads to the gradual emergence of homogeneous VISA. However, *in vitro* studies aimed at testing this hypothesis have produced discordant results (Turner 2001). Recent data suggest that the frequency of hVISA in the United States is low (0.3%) (Richter 2011). The genetic basis of the VISA phenotype is not yet well characterized.

Dalbavancin Resistance in Staphylococci

One of the objectives of the research program leading to the synthesis of dalbavancin was improvement in activity against staphylococci, and in particular against strains resistant to or with reduced susceptibility to teicoplanin. CoNS tested were susceptible to dalbavancin, regardless of species and susceptibility to vancomycin or teicoplanin.

Among *S. aureus*, VISA strains tested were more susceptible to dalbavancin. In one study that included 25 VISA isolates (Report VER001-MI-004), the highest MIC reported was 1 µg/mL and the MIC range was 0.06-1 µg/mL. In a recent study, 36 hVISA MRSA isolates (phenotype confirmed by population analysis) had vancomycin MICs of 1-2 µg/mL and teicoplanin MICs of 1–4 µg/mL. Against these strains, dalbavancin MIC values were 0.03-0.12 µg/mL (Campanile 2010). In another study, in which population analysis of dalbavancin susceptibility was performed against 32 MRSA, including a number of hVISA strains, subpopulations with reduced dalbavancin susceptibility were not observed (Report XRES-05062013).

Only the first two VRSA strains isolated have been tested for susceptibility to dalbavancin. The second VRSA isolate was from Hershey, Pennsylvania; despite carrying *vanA* genetic determinants, it is not phenotypically VanA (i.e., it is teicoplanin-susceptible). Consistent with this observation, the dalbavancin MIC for this strain, as initially isolated, was 0.5 µg/mL (Bozdogan 2003). However, dalbavancin had reduced potency against the Michigan VRSA strain (MIC=16 µg/mL) (Report VER001-MI-004), and the same would be expected for other VRSA that are resistant to both teicoplanin and vancomycin.

Lack of Resistance Development to Dalbavancin *in Vitro*

High-level glycopeptide resistance, affecting both vancomycin and teicoplanin, requires the presence and expression of the *vanA* gene cluster, consisting of several genes needed to substitute the altered cell wall precursor depsipeptide D-ala-D-lac for the normal peptide D-ala-D-ala as well as regulatory genes that respond to both glycopeptides. Multi-genic resistance of

this type cannot simply be selected by exposure to glycopeptides, but requires the presence of another organism that already possesses these determinants and can transfer them.

The development of resistance (i.e., stably increased MIC) in bacteria exposed to dalbavancin *in vitro* or in animal infection studies has not been observed. Among more than 60,000 *S. aureus* strains tested in surveillance studies, resistance to dalbavancin was not detected.

Lack of ready development of resistance to dalbavancin *in vitro* has been demonstrated by means of direct selection and serial passage experiments conducted with a number of staphylococcal isolates in three different laboratories (Report XRES-05062013, Report DAL02M-002, Report VER001-MI-012, Report VER001-MI-003, Lopez 2005). Importantly, no increase in dalbavancin MIC was seen with a VISA strain, either in serial passage or direct plating experiments. In a study of 32 MDR-MRSA strains, including 12 confirmed hVISA strains, only five strains had small frequencies of sub-clones that grew on agar with 2 µg/mL of dalbavancin (Report XRES-05062013), while these same strains showed growth on high concentrations of vancomycin and/or at high frequency. Additionally, when two of the susceptible strains were passaged daily for seven days, no colonies with increased dalbavancin MIC were obtained. These results suggest a low potential for resistance development to dalbavancin.

Additionally, no emergence of resistance to dalbavancin was detected in animal infection experiments or *in vitro* studies designed to detect development of resistance or heterogeneous susceptibility. Thus, the potential for emergence of resistance to dalbavancin in target organisms appears to be low.

SPECTRUM OF ACTIVITY

Evaluation of the *in vitro* potency of dalbavancin has been conducted with more than 150,000 clinical isolates of Gram-positive bacteria from hundreds of centers worldwide. More than 70,000 of these represent worldwide surveillance isolates collected from 2007 through 2012. MICs were determined in comparison with currently available antibacterial agents and were quality controlled using reference strains. Dalbavancin demonstrated potent activity against Gram positive bacteria that are significant abSSSI pathogens, as well as against several other groups of organisms. In general, dalbavancin had greater *in vitro* potency than other glycopeptides and most other classes of comparators tested. Strains resistant to other classes of antimicrobials currently used to treat Gram-positive infections were susceptible to dalbavancin.

Methods for Assessment of *in Vitro* Activity

The principal target pathogens in abSSSI are staphylococci and streptococci. Broth microdilution, with CLSI methodology (CLSI 2012a, CLSI 2013), was used as the standard for determining activity of antibacterial agents against bacteria that grow aerobically. Testing was

conducted in a number of laboratories, using freshly prepared, frozen or commercially prepared dry-form MIC panels. CLSI-specified media for staphylococci and streptococci were utilized. The MICs of dalbavancin for anaerobes were determined using the CLSI agar dilution method (CLSI 2012b). Agar dilution methodology has not been standardized for dalbavancin and is not recommended for testing aerobic bacteria, as the potency of dalbavancin appears to be lower and more variable than by broth microdilution.

Analytical studies demonstrated that the solubility limit of dalbavancin at neutral pH (such as in broth media) was approximately 20 µg/mL. Therefore, using the standard dilution scale, the maximum concentration of dalbavancin that should be tested is 16 µg/mL. In order to ensure solubility of all dilutions, DMSO is used as the intermediate diluent for dalbavancin (CLSI 2012a, CLSI 2013).

During the course of development of dalbavancin, dry-form and frozen microtiter trays were utilized. It was observed that a small amount of a detergent, such as polysorbate-80 (P-80 or Tween 80), when included in the inoculum and diluent, ensured more reproducible dalbavancin MICs for quality control (QC) strains and other isolates when using the frozen panels. Use of P-80 in the inoculum water has been standard practice in many laboratories since the microdilution method for MIC determination was first validated (Barry 1978), and does not appear to affect the potency of most other antimicrobial agents. The methodology for dalbavancin has now been standardized to include 0.002% P-80 in the dalbavancin dilution series rather than introducing it in the inoculum.

***In Vitro* Activity of Dalbavancin in Non-Clinical Microbiology Studies**

Prospective worldwide surveillance of the *in vitro* potency of dalbavancin, in comparison with other antimicrobial agents, was begun in 2002 and has continued through 2012. More than 150,000 Gram-positive isolates were collected, mainly (>125,000) from patients in the United States and Europe. Over 70,000 of the isolates were from 2007 through 2012. The emphasis, particularly in recent years, has been on the species that are most relevant to the proposed indication, abSSSI. Overall, more than 60,000 of the surveillance isolates were *S. aureus* and more than 7,000 were β-hemolytic streptococci. Additionally, the potency of dalbavancin against collections of specific organism categories was examined in a number of studies.

SURVEILLANCE STUDIES

The most extensive surveillance study of dalbavancin activity is the SENTRY study, which has been continuing, prospectively, since 2002. Other prospective surveillance studies have been conducted in Europe, Canada and a few other countries. Additionally, there have been retrospective studies in which large culture collections were sampled, sometimes with the inclusion of challenge isolates.

SENTRY Study

The potency of dalbavancin and selected comparators against Gram-positive aerobic bacteria has been evaluated in an ongoing prospective worldwide surveillance study initiated in 2002 (the SENTRY study, conducted by JMI Laboratories, North Liberty, Iowa USA). This program collects isolates from several hundred hospitals. Most of the data available, through 2012, are for isolates from the United States and Europe. All of the strains tested were unique patient isolates; the sources were mainly bloodstream, respiratory and SSSI infections. Isolates were tested by the broth microdilution method (CLSI 2012a, CLSI 2013) using validated dry-form microtiter panels (Jones 2004).

Susceptibility data is available for more than 126,000 isolates of Gram-positive aerobic cocci, including more than 60,000 *S. aureus* and more than 7,000 β-hemolytic streptococci. Over 70,000 of the isolates were collected between 2007 and 2012. In this and several other studies to be described, the activity of dalbavancin was compared to that of a number of other antibacterial agents that are utilized to treat Gram-positive infections, including the glycopeptides vancomycin and teicoplanin. The lipopeptide daptomycin was included when it became available.

Dalbavancin had potent activity against the major classes of organisms included in the surveillance study. Its potency was maintained from 2002 through 2012, with no shifts in MIC distribution. The following tables summarize the MIC distribution in each year for US isolates of different organisms; the majority of the data, as well as the most recent available data, are for strains isolated in the US.

Trends in Dalbavancin Potency in the US

The MIC distributions, by year, for a total of nearly 40,000 *S. aureus* isolates are presented in Table 1.

Table 1. Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin MICs against *S. aureus* from the USA

Year (No. Tested)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	0.5	50%	90%
2002 (1817)	579	1194	39	4	1	0.06	0.06
2003 (1326)	646	655	23	2	--	0.06	0.06
2004 (2442)	1095	1301	42	3	1	0.06	0.06
2005 (3618)	1369	2127	119	3	--	0.06	0.06
2006 (5713)	2074	3409	216	13	1	0.06	0.06
2007 (6111)	819	4663	612	17	--	0.06	0.12
2008 (5610)	519	4218	835	38	--	0.06	0.12
2009 (4990)	504	3775	660	51	--	0.06	0.12
2010 (6161)	2354	3592	195	20	--	0.06	0.06

2011 (1036)	391	611	32	2	--	0.06	0.06
2012 (1000)	192	716	91	1	--	0.06	0.06
All (39,824)	10,542 (26.5)a	26,261 (65.9)	2,864 (7.2)	154 (0.4)	3 (<0.1)	0.06	0.06

a Percentage of all strains in parenthesis.
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 6, Microbiology section, this submission.

Reviewer's comments: The MIC90 values for dalbavancin for *S. aureus* isolates were 0.06 µg/mL in 8 of the 11 years of the study (including 2010-2012) and were 0.12 µg/mL for isolates from the other three years. The MIC range extended from ≤ 0.03 to 0.25 µg/mL most years except 2002, 2004 and 2006 when the upper limit was 0.5 µg/mL.

More than half of the US *S. aureus* surveillance isolates were methicillin-resistant. Data for the MSSA and MRSA subsets are presented in Table 2 and Table 3, respectively. The dalbavancin MIC distributions over time are the same for MSSA and MRSA.

Table 2. Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin MICs against Methicillin-Susceptible *S. aureus* from the USA

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 (514)a	193	304	15	2	--	0.06	0.06
2012 (500)a	108	350	42	--	--	0.06	0.06
All (18,934)	5,250 (27.7)a	12,284 (64.9)	1,336 (7.1)	64 (0.3)	--	0.06	0.06

a Percentage of all strains in parenthesis.
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 7, Microbiology section, this submission.

Reviewer's comments: The MIC90 values for dalbavancin for MSSA isolates were 0.06 µg/mL in 8 of the 11 years of the study (including 2010-2012) and were 0.12 µg/mL for isolates from the other three years. The MIC range extended from ≤ 0.03 to 0.25 µg/mL most years except 2005 and 2012 when the upper limit was 0.12 µg/mL.

Table 3. Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin MICs against Methicillin-Resistant *S. aureus* from the USA

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 (522)a	198	307	17	--	--	0.06	0.06
2012 (500)a	84	366	49	1	--	0.06	0.06
All (20,890)	5,292 (25.3)a	13,977 (66.9)	1,528 (7.3)	90 (0.4)	3 (<0.1)	0.06	0.06

a Percentage of all strains in parenthesis.
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 8, Microbiology section, this submission.

Reviewer's comments: The MIC90 values for dalbavancin for MRSA isolates were 0.06 µg/mL in 9 of the 11 years of the study (including 2010-2012) and were 0.12 µg/mL for isolates from the other two years. The MIC range extended from ≤ 0.03 to 0.25 µg/mL most years except 2002, 2004, 2006 and 2011 when the upper limit was 0.5 µg/mL for the even numbered years and 0.12 µg/mL for 2011.

The potency of dalbavancin against CoNS is very similar to what is reported for *S. aureus*. Surveillance data for 7,016 CoNS isolates was collected during the 9-year period 2002-2010 (Table 4).

Table 4. Nine-Year (2002-2010) Surveillance Trends in Dalbavancin Potency against Coagulase-Negative Staphylococci from the USA

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
All (7,016)	3,405 (48.5)a	2,701 (38.5)	743 (10.6)	142 (2.0)	20 (0.3)	5 (<0.1)	0.06	0.12

a Percentage of all strains in parenthesis. Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 9, Microbiology section, this submission.

Reviewer's comments: Surveillance studies of the MIC90 values against coagulase negative staphylococci were 0.06 or 0.12 µg/mL (overall, 0.12 µg/mL). The MIC range extended from ≤ 0.03 to 1 µg/mL most years.

Among the β-hemolytic streptococci tested, susceptibility data are presented for US isolates of *S. pyogenes* (N=2,051, Table 5) and *S. agalactiae* (N=2,700, Table 6). These organisms are highly susceptible to dalbavancin.

Table 5. Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin MICs against *S. pyogenes* from the USA

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 (155)a	143	11	1	--	--	≤0.03	≤0.03
2012 (151)a	145	5	1	--	--	≤0.03	≤0.03
All (2,051)	1,999 (97.5)a	47 (2.3)	5 (0.2)	--	--	≤0.03	≤0.03

a Percentage of all strains in parenthesis.
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 10, Microbiology section, this submission.

Table 6. Eleven-Year (2002-2012) Surveillance Trends in Dalbavancin MICs against *S. agalactiae* from the USA

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 (153)a	78	41	20	14	--	≤0.03	0.12
2012 (134)a	118	11	3	2	--	≤0.03	0.06
All (2,700)	2,242 (83.0)a	305 (11.3)	104 (3.9)	49 (1.8)	--	≤0.03	0.06

a Percentage of all strains in parenthesis.
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 11, Microbiology section, this submission.

Reviewer's comments: The dalbavancin MIC90s for *S. pyogenes* were ≤0.03 µg/mL for all years. The MIC range extended from ≤ 0.03 to 1 µg/mL most years. The dalbavancin MIC90s for *S. agalactiae* ranged between ≤ 0.03 and 0.12 µg/mL with an overall MIC90 of 0.06 µg/mL. The MIC range was from ≤ 0.03 µg/mL to an upper limit of 0.25 µg/mL most years.

From 2002 through 2010, nearly 2,000 viridans group streptococci from the US were included in the dalbavancin surveillance database, as shown in Table 7.

Table 7. Nine-Year (2002-2010) Surveillance Trends in Dalbavancin MICs against Viridans Group Streptococci from the USA

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
All (1,974)	1,774 (89.9)a	175 (8.9)	22 (1.1)	3 (0.2)	--	0.06	0.06

a Percentage of all strains in parenthesis.
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 12, Microbiology section, this submission.

Reviewer's comments: The MIC90s for viridans *Streptococci* were initially ≤0.03 µg/mL and then increased to 0.06 µg/mL in 2008 and remained there. The MIC range extended from ≤ 0.03 to 0.25 µg/mL over time. There was considerable variation in the upper limit of the MIC range over time. The upper limit ranged from ≤ 0.03 µg/mL in 2002 and 2003 to 0.06 µg/mL in 2004 to 0.12 µg/mL in 2005—2008 to 0.25 µg/mL in 2009 and 2010.

From 2002 through 2010, 9,503 *S. pneumoniae* isolates were included in the surveillance study (Table 13, this submission, not shown). The MIC90 for this organism was consistently ≤0.03 µg/mL. The upper limit of the MIC range varied from 0.06 µg/mL in 2002, 2003, 2007 and 2008 to 0.12 µg/mL in 2009 and 2010 to 0.25 µg/mL in 2004 and 2005.

The dalbavancin MIC distributions for 7,456 *E. faecalis* US isolates are in Table 8.

Table 8. Nine-Year (2002-2010) Surveillance Trends in Dalbavancin Potency against *E. faecalis* from the USA

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
All (7,456)	3,196 (42.9)a	3,549 (47.6)	402 (5.4)	28 (0.4)	5 (<0.1)	5 (<0.1)	8 (0.1)	263 (3.5)	0.06	0.06

a Percentage of all strains in parenthesis.
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 14, Microbiology section, this submission.

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 in Table 9.

Table 9. Summary of Nine-Year (2002-2010) Surveillance Data for Dalbavancin Potency against US Isolates of *E. faecium* (Vancomycin-Susceptible and –Resistant Subsets) and Vancomycin-Resistant *E. faecalis*

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 R. Jones, JMI Laboratories, SENTRY database.
Source: Table 15, Microbiology section, this submission.

Reviewer's comments: From 2002 through 2010, 7,456 *E. faecalis* US isolates were included in the surveillance study (Table 14, this submission, not shown). The overall MIC90 of dalbavancin was 0.06 µg/mL although it varied from year to year from 0.06 µg/mL to 0.12 µg/mL. The MIC range was from ≤ 0.03 µg/mL to an upper limit of ≥ 4 µg/mL.

The overall dalbavancin MIC distributions (2002-2010) for US isolates of vancomycin-susceptible *E. faecium* (961 isolates), vancomycin-resistant *E. faecium* (3029 isolates) and vancomycin-resistant *E. faecalis* (347 isolates) were included in the surveillance study (Table 15, this submission, not shown). MIC90 values for *E. faecium* VanS, *E. faecium* VanR and *E. faecalis* VanR were 0.12, ≥ 4 and ≥ 4 µg/mL, respectively. For all three strains, the MIC range was ≤ 0.03 µg/mL to an upper limit of ≥ 4 µg/mL.

Comparison of Overall Susceptibility to Dalbavancin in Europe and the US

Between 2002 and 2010, approximately 51,500 isolates from Europe were included in the dalbavancin surveillance database, for a total of nearly 124,000 strains when combined with US data collected over the same period for the major groups of aerobic Gram-positive cocci (data not shown).

Reviewer's comments: The details of these data are not presented here but are summarized as follows. The MIC90s from US and European isolates of staphylococci, streptococci and enterococci were nearly identical. The exception was the MIC90 for viridans streptococci from the US were one dilution step higher (0.06 µg/mL).

Dalbavancin Potency Compared with Other Antimicrobial Agents

The following tables compare the activity of dalbavancin and other agents vs. US surveillance isolates. For comparators, the percent susceptibility, intermediate susceptibility and resistance

according to US (CLSI) and European (EUCAST) criteria are included, when available. The data for *S. aureus* are in Table 10.

Table 10. Comparative Activity of Dalbavancin against 39,824 Isolates of *S. aureus* from the US (2002-2012)

Antimicrobial Agent	MIC (µg/mL)			%S / %I / %R[a]	
	50%	90%	Range	CLSI	EUCAST
Dalbavancin	0.06	0.06	≤0.03 – 0.5	- / - / -	- / - / -
Vancomycin	1	1	≤0.12 – 4	>99.9 / <0.1 / 0.0	>99.9 / 0.0 / <0.1
Teicoplanin	≤ 2	≤ 2	≤2 – 8	100.0 / 0.0 / 0.0	99.7 / 0.0 / 0.3
Oxacillin	> 2	> 2	≤0.25 – >2	47.5 / 0.0 / 52.5	47.5 / 0.0 / 52.5
Erythromycin	> 2	>2	≤0.25 – >2	35.9 / 0.9 / 63.2	36.1 / 0.4 / 63.5
Clindamycin	≤ 0.25	>2	≤0.25 – >2	76.5 / 0.2 / 23.3	76.1 / 0.4 / 23.5
Daptomycin	0.25	0.5	≤0.12 – 4	99.9 / - / -	99.9 / 0.0 / 0.1
Levofloxacin	≤ 0.5	> 4	≤0.5 – >4	56.6 / 1.1 / 42.3	56.6 / 1.1 / 42.3
Linezolid	1	2	≤0.25 – >8	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
Tetracycline	≤ 4	≤ 4	≤4 – >8	95.1 / 0.5 / 4.4	89.7 / 0.4 / 9.9

a Criteria as published by CLSI 2013 and EUCAST (2013)
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 18, Microbiology section, this submission.

Reviewer's comments: Dalbavancin had the lowest MIC90 of any antibiotic against *S. aureus*. The next lowest MIC90 was for daptomycin (0.5 µg/mL) and the highest was for levofloxacin (>4 µg/mL). By both CLSI and EUCAST criteria, 52.5% of the *S. aureus* isolates were methicillin resistant, based on oxacillin MIC data. By CLSI criteria, there were no glycopeptide-resistant or –intermediate *S. aureus* isolates, whereas by EUCAST criteria there were a small number of isolates with intermediate susceptibility to vancomycin (VISA; <0.1%) or teicoplanin (0.3%).

Susceptibility data for β-hemolytic streptococci (which were mainly *S. pyogenes* and *S. agalactiae*) are shown in Table 11.

Table 11. Comparative Activity of Dalbavancin against 4,802 Isolates of β-Hemolytic Streptococci from the US (2002-2012)

Antimicrobial Agent	MIC (µg/mL)			%S /%I / %Ra	
	50%	90%	Range	CLSI	EUCAST
Dalbavancin	≤0.03	0.06	≤0.03–0.25	- / - / -	- / - / -
Vancomycin	0.5	0.5	≤0.12 – 1	100.0 / - / -	100.0 / 0.0 / 0.0
Penicillin	≤0.06	≤0.06	≤0.06–0.25	>99.9 / - / -	100.0 / 0.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25–2	99.9 / - / -	100.0/<0.1/0.0
Erythromycin	≤0.25	>2	≤0.25–>2	68.9/0.7/30.4	68.9 / 0.7 / 30.4
Clindamycin	≤0.25	>2	≤0.25–>2	84.7/0.4/14.9	85.1 / 0.0 / 14.9

Daptomycin	≤0.12	0.25	≤0.12–0.5	100.0 / - / -	100.0 / 0.0 / 0.0
Levofloxacin	≤0.5	1	≤0.5 – >4	99.1 / 0.1 / 0.8	96.0 / 3.1 / 0.9
Linezolid	1	1	≤0.12 – 2	100.0 / - / -	100.0 / 0.0 / 0.0
Tetracycline	>8	>8	≤4 – >8	45.1 / 1.5 / 53.4	44.9 / 0.2 / 54.9
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	- / - / -	98.5 / 0.4 / 1.1

Abbreviations: S=Susceptible; I=Intermediate; R=Resistant; TMP/SMX=trimethoprim/sulfamethoxazole.
a Criteria as published by CLSI (2013) and EUCAST (2013)
Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 20, Microbiology section, this submission.

Reviewer's comments: Dalbavancin had greater potency against beta hemolytic streptococci than the comparators, with the exception of penicillin, which had a similar MIC range and MIC90. The next lowest MIC90 was found for ceftriaxone. The highest MIC90 values were seen for tetracycline. High levels of resistance was observed for erythromycin (30.4%), clindamycin (14.9%) and tetracycline (>50%).

Dalbavancin had more potent activity against viridans group streptococci (N=1,974) than all of the comparators Table 12.

Table 12. Comparative Activity of Dalbavancin against 1,974 Isolates of Viridans Group Streptococci from the US (2002-2010[a])

Antimicrobial Agent	MIC (µg/mL)			%S /%I / %R[b]	
	50%	90%	Range	CLSI	EUCAST
Dalbavancin	≤0.03	0.06	≤0.03–0.25	- / -/ -	- / -/ -
Vancomycin	0.5	0.5	≤0.12–2	99.9 / -/ -	100.0/0.0/0.0
Penicillin	≤0.06	1	≤0.06– >4	73.9/22.0/4.1	82.2/13.7/4.1
Ceftriaxone	≤0.25	1	≤0.25 – 32	93.4 / 3.6 / 3.0	88.6 / 0.0 / 11.4
Erythromycin	1	>2	≤0.25 – >2	46.2 / 2.7 / 51.1	- / -/ -
Clindamycin	≤0.25	0.5	≤0.25 – >2	89.5 / 1.0 / 9.5	90.5 / 0.0 / 9.5
Daptomycin	0.25	0.5	≤0.12 – 4	99.7 / -/ -	- / -/ -
Levofloxacin	1	2	≤0.5 – >4	91.7 / 1.1 / 7.2	- / -/ -
Linezolid	1	1	≤0.25 – 8	99.9 / -/ -	- / -/ -
Tetracycline	≤4	>8	≤4 – >8	61.8 / 4.8 / 33.4	- / -/ -
TMP/SMX	≤0.5	>2	≤0.5 – >2	- / -/ -	- / -/ -

Abbreviations: S=Susceptible; I=Intermediate; R=Resistant; TMP/SMX=trimethoprim/sulfamethoxazole.
a Includes: *Streptococcus acidominimus* (1 strain), *Streptococcus anginosus* (105 strains), *Streptococcus bovis* group (98 strains), *Streptococcus canis* (2 strains), *Streptococcus constellatus* (55 strains), *Streptococcus cristatus* (1 strain), *Streptococcus equinus* (1 strain), *Streptococcus gallolyticus* (17 strains), *Streptococcus gordonii* (14 strains), *Streptococcus infantarius* (2 strains), *Streptococcus intermedius* (37 strains), *Streptococcus milleri* (54 strains), *Streptococcus mitis* (276 strains), *Streptococcus mutans* (10 strains), *Streptococcus oralis* (36 strains), *Streptococcus parasanguinis* (44 strains), *Streptococcus pasteurianus* (1 strain), *Streptococcus porcinus* (2 strains), *Streptococcus salivarius* (67 strains), *Streptococcus sanguinis* (62 strains), *Streptococcus thermophilus* (1 strain), *Streptococcus uberis* (4 strains), *Streptococcus vestibularis* (6 strains), unspeciated *Streptococcus* (3 strains), unspeciated alpha-haemolyticus streptococci (50 strains), and unspeciated viridans group streptococci (1025 strains).
b Criteria as published by CLSI (2013) and EUCAST (2013)

Data from R. Jones, JMI Laboratories, SENTRY database.
Source: Table 21, Microbiology section, this submission.

Reviewer's comments: Dalbavancin had greater potency against viridans streptococci than any of the comparators with a MIC90 value of 0.06 µg/mL. The next lowest MIC90 value was found for vancomycin, clindamycin and daptomycin (MIC90=0.5 µg/mL). the highest MIC90 value was found for tetracycline (>8 µg/mL). A high frequency of resistance, by CLSI criteria, was seen with erythromycin (51%) and tetracycline (33%).

Activity of Dalbavancin against Gram-Negative Bacteria

Although in general glycopeptide antibiotics do not have activity against Gram-negative bacteria, dalbavancin (and the parent natural glycopeptide A-40926) has *in vitro* activity against certain fastidious Gram-negative bacteria.

***In Vitro* Activity of Dalbavancin against Bacteria Resistant to Other Classes of Antimicrobial Agents or with Reduced Susceptibility to Glycopeptides**

The surveillance and other studies discussed earlier included thousands of isolates of Gram-positive cocci with resistance phenotypes commonly encountered in the clinic. Among organisms causing abSSSI, MRSA is the most frequently encountered resistance phenotype. MRSA are highly prevalent worldwide and are usually resistant to multiple antibiotic classes including fluoroquinolones and clindamycin. The potent activity of dalbavancin against MRSA (equivalent to its activity against methicillin-susceptible staphylococci) was demonstrated against tens of thousands of clinical isolates in a number of studies, principally the SENTRY data base. These isolates were largely from skin and other serious infections, and from hospitals worldwide, in particular from the US and Europe. Potent activity of dalbavancin against erythromycin-resistant *S. pyogenes*, as well as β-lactam-resistant streptococci (pneumococci and viridans group streptococci) was also demonstrated in several of these studies. Other studies were designed to challenge dalbavancin by testing its activity against more novel resistance phenotypes (e.g., to more recently introduced antimicrobial agents) and against MDR isolates.

The spectrum of activity of dalbavancin includes most species of Gram-positive bacteria implicated in abSSSI.

Prospective worldwide surveillance of the *in vitro* potency of dalbavancin, in comparison with other antimicrobial agents, was begun in 2002 and has continued through 2012, with several thousand Gram-positive clinical isolates (principally staphylococci, streptococci and enterococci) tested in most years. The emphasis has been on species that are relevant to the proposed indication, acute bacterial skin and skin structure infection (abSSSI), including methicillin-resistant *Staphylococcus aureus* (MRSA) and multiply resistant isolates. Additionally,

the potency of dalbavancin against collections of specific organism categories was examined in a number of studies.

Using a validated broth microdilution method, dalbavancin minimal inhibitory concentration (MIC) ranges for aerobic Gram-positive cocci were very narrow and the MIC90 (MIC for at least 90% of strains tested) ranged from ≤0.03 to 0.12 µg/mL for most species. Dalbavancin demonstrated greater *in vitro* potency than currently available glycopeptides and most other comparators. The activity of dalbavancin is not affected by resistance to other classes of antibacterial agents.

Dalbavancin demonstrates greater *in vitro* potency against some organisms that are resistant to vancomycin or teicoplanin, including coagulase-negative staphylococci (CoNS) resistant to or with reduced susceptibility to teicoplanin. In one study of 25 vancomycin-intermediate (VISA) and heterogeneously vancomycin-intermediate (hVISA) *S. aureus* isolates, all MIC values of dalbavancin were ≤1 µg/mL. In other studies, dalbavancin MICs for 36 hVISA strains were 0.03-0.12 µg/mL (Campanile 2010), and heterogeneous resistance to dalbavancin was not detected among 32 MRSA strains, including both vancomycin-susceptible and hVISA strains (Report XRES 05062013). In a study of 20 isolates of CoNS with reduced susceptibility to teicoplanin (MIC>8 µg/mL), dalbavancin MIC values were 0.03-0.12 µg/mL. Among >7,000 CoNS from the SENTRY data base, which included approximately 10% of isolates considered to be teicoplanin-resistant by EUCAST criteria, all isolates were susceptible to ≤1 µg/mL of dalbavancin and 99.6% of all isolates were susceptible to ≤0.25 µg/mL. Resistance to dalbavancin among Gram-positive bacteria appears to be limited to certain intrinsically glycopeptide-resistant species and to bacteria expressing the VanA phenotype of acquired resistance. Dalbavancin, like teicoplanin, is active against the intrinsically vancomycin-resistant enterococcal species expressing the VanC phenotype and against VanB strains with acquired resistance, but is not active against other intrinsically glycopeptide-resistant Gram-positive species such as pediococci, leuconostocs and some species of lactobacilli. Like other glycopeptides, dalbavancin is not generally active against Gram-negative bacteria; however *in vitro* activity against certain fastidious Gram-negative species such as *Neisseria gonorrhoeae* and *Moraxella catarrhalis* has been reported.

BACTERICIDAL ACTIVITY

Dalbavancin is bactericidal for target organisms *in vitro* at concentrations of free drug that are sustained in human plasma throughout the one-week dosing interval. Dalbavancin is more consistently bactericidal than vancomycin or teicoplanin. Studies of the bactericidal activity of dalbavancin have included determination of minimal bactericidal concentration (MBC) and time kill experiments. The *in vitro* bactericidal activity of dalbavancin is time-dependent, similarly to conventional glycopeptides such as vancomycin and teicoplanin. Dalbavancin has also shown bactericidal activity in animal infection models.

Minimal Bactericidal Concentration

The MBC is a rapid method for estimating bactericidal activity, because it consists of simply plating the contents of clear wells after MIC determination by the broth microdilution method.

The MBC is usually arbitrarily defined as the lowest concentration of an antibiotic needed to kill 99.9% of viable organisms after exposure for 24 hours. The accuracy of this method is limited because of the low number of CFU on which it is based; in some cases presence or absence of one or a few colonies may determine the MBC. Based on the Poisson distribution, statistical tables of cut-off values for 99.9% kill (based on pipetting errors, inoculum and sample size) have been published (Pearson 1980), but these corrections are rarely applied in practice; therefore, on average, the percent kill may be under-estimated and thus the MBC may be over-estimated.

In the case of dalbavancin, sticking to plastic surfaces is a problem, as in MIC determination. Studies in which precautions have been taken to ensure solubility and to prevent dalbavancin from sticking to plastic surfaces demonstrated dalbavancin MBC values to be close to the MIC values for most staphylococcal and streptococcal isolates tested. As discussed above, the methodology utilized may tend to inflate the MBC values; the extent of the error might be higher for agents having time-dependent bactericidal activity.

There is variability in MBC/MIC ratios among strains of the same species in the absence of P-80. There is a trend toward higher ratios at lower MIC values. This may be because longer exposure of dalbavancin to plastic in the absence of P-80 leads to progressive loss of dalbavancin activity from solution (Rennie 2007), which might lead to some re-growth. The fraction of dalbavancin lost from solution is higher when the initial concentration is lower.

Time Kill Studies

Time-kill studies generally utilize a higher inoculum, which provides a more reliable estimate of the extent of bacterial killing than in MBC determinations. The bactericidal activity of dalbavancin was also assessed in several time-kill studies (Candiani 1999, Jones 2001, Bozdogan 2003, Report DAL02M-002, Lopez 2005, Report VER001-MI-011, Lin 2005a, Lin 2005b). Dalbavancin is bactericidal for target organisms at concentrations that are sustained in human plasma over the dosing interval with proposed regimens. Results were similar in experiments based on total drug concentrations in the presence of 50% human serum, and in experiments using estimated unbound drug concentrations in the absence of serum. Using concentrations spanning estimated unbound dalbavancin concentrations, time-dependent bactericidal activity was observed.

In general, just as MICs are about 4-fold lower when appropriate conditions are used to ensure its *in vitro* availability, killing by dalbavancin is observed at lower concentrations when using

either a wetting agent (in time-kill experiments) or dry-form microtiter trays (for MBC determination).

POST-ANTIBIOTIC EFFECT

The post-antibiotic effect (PAE) is defined as suppression of bacterial growth that persists after organisms have been exposed to an antimicrobial agent and the agent has then been removed. Generally, an increase of 1 log10 in CFU/mL from the time the antimicrobial agent is removed is used to define the end of the post-antibiotic interval and the PAE (T-C) is then calculated as the difference between the times required for the treated culture (T) and the untreated control (C) to increase by 1 log10 CFU/mL.

The *in vitro* PAE of dalbavancin was determined against four strains of *S. aureus*, which included a MSSA strain, a MRSA strain and 2 VISA isolates (Report DAL02M-002). Briefly, log phase organisms were grown in CAMHB and first exposed to 4X MIC of dalbavancin, vancomycin or teicoplanin for one hour at 35°C in a shaking incubator. Test tubes were sampled immediately after addition of antibiotic and one hour later. Drug-free control and treated cultures were then diluted 500-fold in fresh pre--warmed medium without antibiotic to allow growth to resume and tittered each hour. The PAE for both dalbavancin and teicoplanin ranged from about 1 to 3 hours, and for vancomycin was approximately 2 hours (Report DAL02M-002). The relatively short PAE for dalbavancin, typical for glycopeptides, is unlikely to be a significant factor *in vivo* because of the long $t_{1/2}$ of dalbavancin.

INTERACTIONS WITH OTHER ANTIMICROBIALS

In experiments *in vitro* with several species of bacteria, no antagonism was observed when dalbavancin was combined with other antimicrobial agents that are used to treat Gram-positive and Gram-negative infections. No antagonism has been observed *in vitro* between dalbavancin and other agents commonly used to treat Gram-positive infections. Potentially useful synergy with oxacillin has been reported against some MRSA and VISA strains and with ampicillin against VanA enterococci. Interactions of vancomycin and teicoplanin with other agents have been extensively investigated, in particular against resistant organisms such as MRSA and VRE, where combination therapy may have advantages. *In vitro* synergy is often observed between glycopeptides and β-lactams or aminoglycosides. Importantly, antagonistic interactions have rarely been observed for the glycopeptide class of antibiotics.

Experiments conducted with dalbavancin indicated that, as expected, there were no antagonistic interactions with a variety of agents that might be used in combination or in sequence to treat Gram-positive infections (Johnson 2006). Lack of *in vitro* antagonism between dalbavancin and other systemically used antimicrobial agents suggests that its use in

combination with or in temporal proximity to another agent should not present a therapeutic concern.

PRECLINICAL EFFICACY—*IN VIVO*

ANIMAL PHARMACODYNAMICS

The time-dependent bactericidal activity of dalbavancin *in vitro* suggested that time above the MIC might be the important PD parameter of efficacy for dalbavancin. In the neutropenic mouse thigh infection model, AUC of unbound drug/MIC correlated best with the efficacy of dalbavancin against *S. aureus* and *S. pneumoniae*. In this and other models, widely spaced, large doses were very effective, supporting the weekly human dosage regimen.

Different types of studies contribute to understanding the PD of dalbavancin, including: *in vitro* studies of its bactericidal activity against target bacteria, modeling of PK and efficacy data in infected and uninfected animals, and detection of bactericidal activity in the serum of human subjects at different times after receiving a dose of dalbavancin.

However, a clear relationship between *in vitro* MIC for particular isolates and efficacy in clinical trials has not been established. Susceptibility breakpoints proposed by the Applicant were based on population PK and target attainment considerations.

OVERVIEW OF ANIMAL PHARMACOKINETICS

Dalbavancin is administered intravenously over 30 minutes in humans, with a unique regimen of 1000 mg on day one and 500 mg on day 8. Because dalbavancin has a predominant half-life of 5-7 days, this regimen provides coverage for a 14-day period. The mean plasma Cmax of dalbavancin is 285 µg/mL and the minimum inter-dose concentration is at least 20 µg/mL. Since dalbavancin is 93% protein-bound in human plasma, the levels of free drug vary between approximately 20 and at least 1.4 µg/mL. These concentrations are well above the MIC90s of target organisms (principally *S. aureus* and β-hemolytic streptococci) and are also above *in vitro* bactericidal concentrations for these organisms. Addition of human serum to the growth medium had a variable effect on the *in vitro* activity of dalbavancin. Assays of serum samples from human subjects demonstrated persistence of bactericidal activity against MRSA for 7 days following doses of ≥500 mg.

Dalbavancin distributes to various tissues, including the skin. The volume of distribution at steady state, 14 L, is consistent with distribution to extracellular fluid. Concentrations of dalbavancin in blister fluid exceeded 30 µg/mL for seven days after administration of a 1000 mg dose.

A small amount of a hydroxylated metabolite is found in the urine of animals and man. Because the metabolite is less active than dalbavancin, and is also not detectable in the blood, it does not contribute to the *in vivo* activity of dalbavancin. Dalbavancin is excreted both in urine and feces (about 20% of the administered dose). Therefore, potential effects on fecal flora were of interest.

Based on blood and tissue levels in man, *in vitro* activity (including bactericidal activity), against target bacteria, and the results of experiments in animals (which demonstrated the efficacy of single or infrequent doses), a weekly dosage regimen was predicted to be efficacious in treating human infections caused by Gram-positive bacteria. Dose-fractionation studies in animal models also demonstrated greater efficacy of large, widely spaced doses.

Activity of Dalbavancin Metabolites and Minor Components

Minor components of dalbavancin active pharmaceutical ingredient (API), as well as metabolites and degradants have equivalent or lower *in vitro* potency as compared with the principal component B0, suggesting that they have little influence on the *in vivo* activity and PD of dalbavancin.

In rats, dogs, and humans, OH-dalbavancin has been observed in urine. The metabolite levels in plasma are low and the metabolite is less active than dalbavancin, suggesting that it has little influence on *in vivo* activity. When tested against a panel of organisms, MIC values of OH-dalbavancin (prepared synthetically) were 2- to 64-fold those of dalbavancin. Peak OH-dalbavancin concentrations (below or close to the limit of quantitation [0.4 µg/mL] in human plasma) are not clinically relevant in terms of antibacterial activity when compared with dalbavancin concentrations at the same time points in rat, dog, and human plasma.

Dalbavancin API consists of five closely related homologues (A0, A1, B0, B1, and B2). B0 is the major component and makes up (b) (4) of the API. The API homologues differ from one another in the length and/or branching of their respective fatty acid side chains on the N-acylaminoglucuronic acid moiety and the presence of an additional methyl group on the N-terminal amino group of the heptapeptide. Additionally, one of the impurities in the drug substance is the mannosyl aglycone (MAG), which is also a degradation product and biotransformation product of dalbavancin. The MIC values of all of the homologues against a set of staphylococcal, streptococcal and enterococcal strains were similar to those of B0 (within one dilution), whereas the activity of MAG was lower.

PHARMACOKINETICS/PHARMACODYNAMICS

Dalbavancin is administered intravenously in humans. The dosage regimen consists of 1000 mg of dalbavancin IV on Day 1 and 500 mg IV on Day 8. This is consistent with its predominant half-

life ($t_{1/2}$ β) of 5-7 days. Bactericidal levels of dalbavancin are maintained throughout the interval between doses, as shown by: the bactericidal activity of dalbavancin *in vitro* in the presence of 50% human serum; the *in vitro* bactericidal activity of concentrations of 'free' dalbavancin that are sustained in plasma and in blister fluid throughout the dosing interval (based on the determined 93% protein binding in human plasma); the serum bactericidal activity determined in samples from human subjects taken up to seven days after administration of dalbavancin.

Animal infection studies demonstrated that single doses of dalbavancin were effective in several models. Dose fractionation studies indicated that infrequent administration was more effective than frequent small doses. In the neutropenic mouse thigh model, area under the concentration time curve (AUC)/MIC was the pharmacodynamic (PD) parameter that best correlated with efficacy.

Dalbavancin is excreted in both urine and feces. In a fecal flora study in human subjects, dalbavancin had very little effect on Gram-positive bacteria, suggesting that it may be inactive in feces (Nord 2006).

PHARMACODYNAMIC MODELING IN MICE

Neutropenic Thigh Model

The neutropenic mouse thigh model lends itself to PD modeling. Efficacy can be examined as a function of MIC, using a series of different strains, and as a function of dosage regimen, by fractionating different total doses of an antibiotic into a series of regimens of varying dosing frequency. Using the PK of the drug in plasma, efficacy can then be analyzed as a function of different PD parameters such as Cmax/MIC, AUC/MIC, or time above MIC (T>MIC).

The principal observations for dalbavancin were 1) with the same total dose, greater efficacy was associated with less frequent administration of larger individual doses rather than more frequent administration of smaller individual doses and 2) the best correlation of efficacy against *S. aureus* was with the AUC/MIC ratio (Report VER001-MI-013).

Neutropenia was induced in Swiss ICR mice and maintained with cyclophosphamide, starting prior to and continuing throughout the experiments. Approximately 10^6 CFU of a test organism, either *S. aureus* or *S. pneumoniae*, were injected into one or both thighs of the mice. Five pneumococcal strains (three of them PRSP) and six staphylococcal strains (including three MRSA) were utilized as test organisms. The dalbavancin MIC values for the *S. pneumoniae* isolates ranged from 0.004 to 0.03 µg/mL and for the *S. aureus* isolates from 0.06 to 0.12 µg/mL (MBCs 0.12-0.5 µg/mL).

Single dose studies, over the dosage range 2.5-80 mg/kg, confirmed that PK in the mouse was linear. Plasma levels were assayed by a microbiological agar diffusion assay, using droplets applied to the surface of seeded plates (test organism *Bacillus subtilis* ATCC 6633). Blood samples were obtained by puncture of the retro-orbital sinus.

Different total dosages of dalbavancin were administered IP; dosages were fractionated in different time intervals in order to relate PD parameters to MICs. Efficacy was determined based on both bacteriostasis and reduction in bacterial load. Four mice were utilized for each experimental condition. Five total dose levels of dalbavancin were administered over a period of 6 days in doubling increments ranging from 0.6125 to 10 mg/kg for the *S. pneumoniae* infection and from 30 to 480 mg/kg for the *S. aureus* infection. Dose intervals were 12, 24, 36 or 72 hours.

The extent of killing of both species was extensive (> 2log10 CFU reduction at the highest doses studied). The extent and rate of killing of *S. pneumoniae* was greater than for *S. aureus*. Three of the five dose levels reduced the organ load of *S. pneumoniae* by nearly 4 log10 CFU in the thighs of infected mice. In general, dose-response curves indicated greater efficacy when larger doses were administered less frequently.

Each dose-response curve was mathematically characterized using a maximum effect model. This methodology uses the Hill equation to estimate, by nonlinear regression, the maximum effect (Emax), the dose (P50) required to achieve 50% of the Emax, and the slope of the dose-response relationship. From these parameters the dose required to produce a net bacteriostatic effect over the 144-hour treatment period, as well as the doses necessary to produce a 1- or 2-log10 reduction in CFU can be calculated (Table 13).

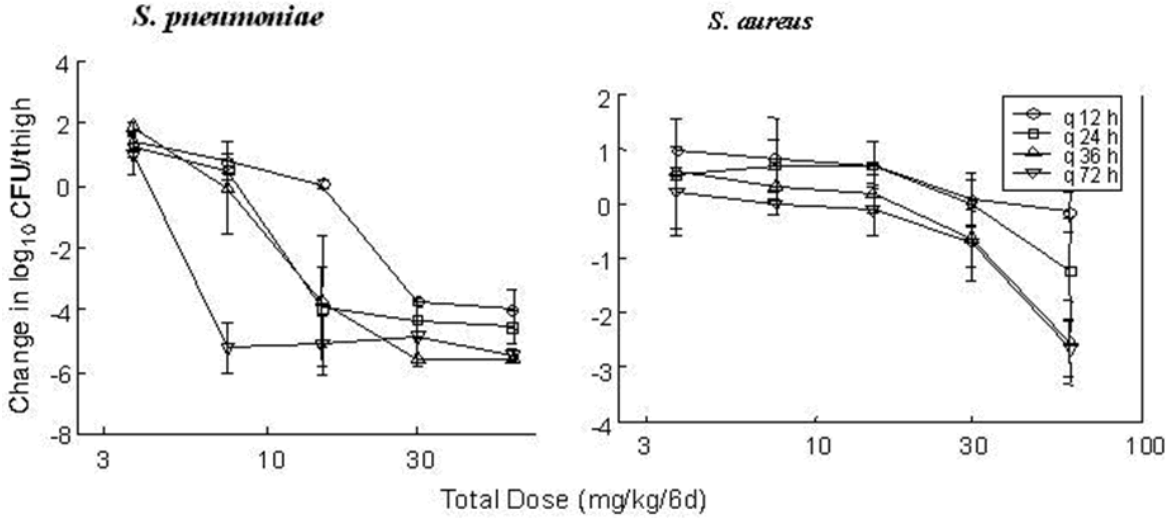
Table 13. Efficacy of Different Dosage Regimens of Dalbavancin against *S. pneumoniae* (SP) and *S. aureus* (SA) in the Neutropenic Mouse Thigh Model

Organism		Static Effect			1-Log Kill			2-Log Kill		
q24 hours regimen	MIC/ MBC (µg/mL)	mg/kg/ 24h	f24 AUC/ MIC	f24 AUC/ MBC	mg/kg/ 24h	f24 AUC/ MIC	f24 AUC/ MBC	mg/kg/ 24h	f24 AUC/ MIC	f24 AUC/ MBC
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	
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								
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	
SA25923	0.12/0.5	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

Source: Table 39, Microbiology section, this submission.

In the *S. pneumoniae* infection, the two highest total doses were effective, regardless of how the dose was divided (Figure 2).

Figure 2. Dose-Effect Relationship with Different Dalbavancin Regimens in the Neutropenic Mouse Thigh Model



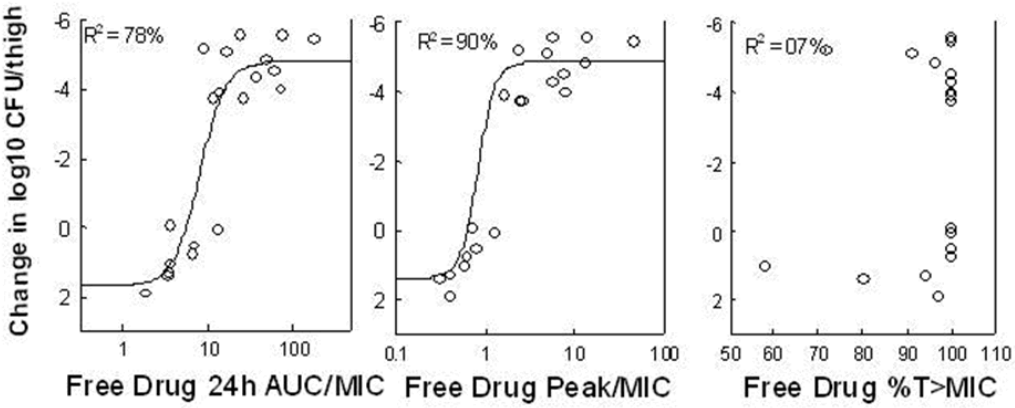
Source: Figure 15, Microbiology section, this submission.

At lower total doses, however, less frequent administration (q 72 hours) of larger amounts of dalbavancin resulted in markedly better killing. Similarly, for *S. aureus*, the two highest total doses were effective with all dosage intervals; however, net reduction in CFU/thigh (1->2 log10 CFU/thigh) was greatest when larger amounts were given less frequently (q 36 or 72 hours) (Figure 2).

In order to correlate PK/PD parameters with free dalbavancin concentration, the impact of drug binding to serum and serum proteins was investigated by comparing *in vitro* inhibition of two strains of *S. aureus* by dalbavancin in broth, serum from infected mice, human serum, and albumin. Based upon the MIC difference between broth and mouse serum, the degree of protein binding was estimated to be 99.6% in the mouse. This degree of binding was used in subsequent PD analyses. For comparison, the degree of binding in human serum was lower, and was estimated to be 96%, similar to the 93% to 95% plasma protein binding reported from experiments conducted with radiolabelled dalbavancin and using more specific dialysis methods.

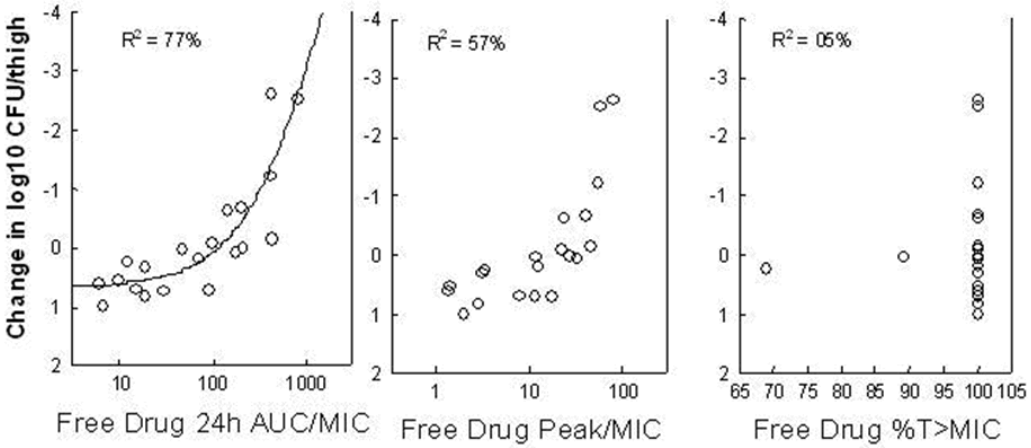
The PK/PD parameter that best correlated with efficacy was determined by relating the CFU/thigh at the end of 144 hours of therapy to the free peak/MIC ratio, the 24-hour free AUC/MIC ratio, and the percentage of the dosing interval over which free serum levels exceeded the MIC (Figures 3 and 4).

Figure 3. Relationship between PK/PD Parameters and Efficacy of Dalbavancin against *S. pneumoniae*



Source: Figure 16, Microbiology section, this submission.

Figure 4. Relationship between PK/PD Parameters and Efficacy of Dalbavancin against *S. aureus*



Source: Figure 17, Microbiology section, this submission.

For both *S. pneumoniae* (Figure 3) and *S. aureus* (Figure 4), a good correlation was observed with the 24-hour AUC/MIC ratio. There was no evident correlation between time above MIC and efficacy; however for *S. aureus*, free drug levels exceeded the MIC for the entire dosing interval for all but two of the 20 different dosage regimens and the remaining two regimens had at least 65% T>MIC and were still bacteriostatic (Figure 3). In the case of *S. pneumoniae*, all but five regimens gave 100% T>MIC (Figure 4). Conclusions regarding lack of correlation with T>MIC are therefore limited by the paucity of data for regimens with lower T>MIC. The total dosage range that was effective for *S. pneumoniae* was lower than for *S. aureus*.

In general, the shape of the dose-response curves was similar for all strains. A single strain of *S. pneumoniae* was tested in both neutropenic and non-neutropenic mice. There was not a statistically significant difference between the two dose-effect curves.

In summary, dalbavancin was bactericidal against both *S. pneumoniae* and *S. aureus* in the murine neutropenic thigh infection model. Its efficacy against both organisms was dose dependent, although for any given total dose, the infrequent administration of larger quantities of drug led to enhanced efficacy as compared with more frequent administration of smaller quantities. Lower doses were effective against *S. pneumoniae* as compared with *S. aureus*. Efficacy was not affected by resistance to β-lactam antibiotics. Against *S. pneumoniae*, neutropenia did not have a significant effect on efficacy. *AUC/MIC was the PK/PD parameter that most closely correlated with efficacy.*

EFFICACY IN ANIMAL INFECTION MODELS

Dalbavancin was efficacious in a number of animal infection studies, at lower and less frequent doses than comparators, and was in some cases efficacious with a single dose. Models included acute septicemia in mice (a prophylaxis model) induced by intraperitoneal (IP) injection of *S. aureus*, *S. pyogenes* and other pathogens, and organ- or site-specific infections such as granuloma pouch (in rats), neutropenic mouse thigh, endocarditis (in rats and rabbits) and pneumonia (in rats). The studies conducted with staphylococci and streptococci are summarized in Table 14 and Table 15, respectively.

Table 14 and Table 15 summarize the animal study data and include the MIC values for the test strains and the highest MIC value in each animal model at which dalbavancin showed efficacy.

Animal studies utilizing staphylococci and streptococci with elevated dalbavancin MICs are limited due to the small number of these organisms that are available and that can be incorporated into recognized animal models. The strain with the highest MIC that was tested in an animal model was a VISA strain (dalbavancin MIC=4 µg/mL, tested without P-80) used in the rabbit endocarditis study. Dalbavancin was efficacious in this model. The Applicant believes the results of animal infection studies with staphylococci and streptococci support a susceptibility breakpoint of 0.25 µg/mL.

Table 14. Dalbavancin: Summary of Animal Infection Model Studies with Staphylococci

Model	Strains Utilized	Dosages	Dosage Frequency	No. of Isolates	MIC (µg/mL)	Highest MIC With Efficacy (µg/mL)
Immunocompetent mouse septicemia, infected IP	MSSA	Varying dosages, SC	Once, 10 min post- infection	1	0.06	0.06
Neutropenic mouse septicemia	*S.epidermidis*	Varying dosages, SC	Once, 10 min post- infection	1	0.12	0.12
Rabbit, left-sided endocarditis	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	MRSA and VISA	40 mg/kg IV	Once, 48 h post-infection	2	MRSA 0.5 VISA 4*	4
Rat, left-sided endocarditis	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	*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	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 0.25-0.5	0.25-0.5
Rabbit, subcutaneous implant	MSSA	10 mg/kg IV	Single pre-operative dose	1	0.06	0.06
Neutropenic mouse, thigh	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	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

Abbreviations: IP=intraperitoneal, IV=intravenous, LD=loading dose, MIC= minimum inhibitory concentration; MRSA= methicillin resistant
Staphylococcus aureus; MSSA= methicillin-sensitive *Staphylococcus aureus*; SC=subcutaneous, qd=once daily
*These MIC values were not determined in the presence of P-80 and are likely over-estimated.
Source: Table 94, Microbiology section, this submission.

Reviewer's comments: The Applicant presents a summary of studies of animal infections with Staphylococci. These animal models include mice, rats and rabbit as well as immunocompetent and neutropenic models. Bacterial strains utilized in these studies were *S. epidermidis* and *S. aureus* (both methicillin susceptible and methicillin resistant). These studies were done in a variety of body sites in animals. The range of highest, efficacious MIC ran from 0.06 mcg/ml in neutropenic mice in the lung due to MSSA and subcutaneous implants in rabbits infected with MSSA to 4 mcg/ml in rabbits with endocarditis infected with MRSA and VISA. (b) (4)

Table 15. Dalbavancin: Summary of Animal Infection Model Studies with Streptococci

Model	Strains Utilized	Dosages	Dosage Frequency	No. of Isolates	MIC (µg/mL)	Highest MIC With Efficacy (µg/mL)
Immunocompetent mouse septicemia, infected IP	*S. pyogenes*	Varying dosages, SC	Once, 10 min post- infection	1	0.06	0.06
Immunocompetent mouse septicemia, infected IP	PSSP	Varying dosages, SC	Once, 10 min post- infection	1	0.03	0.03
Immunocompetent rat, pneumonia	PRSP	10 mg/kg IV	Once, 12 h post- infection	1	0.25	0.25
Immunocompetent and neutropenic rat, lobar pneumonia	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	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	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

Abbreviations: h=hour; IP=intraperitoneal, IV=intravenous, SC=subcutaneous
Source: Table 95, Microbiology section, this submission.

Reviewer's comments: The Applicant presents a summary of studies of animal infections with Streptococci. These animal models include both mice and rats as well as immunocompetent and neutropenic models. Bacterial strains utilized in these studies were *S. pyogenes* and *S. pneumoniae* (both penicillin susceptible and penicillin resistant). These studies were done in a variety of body sites in animals. The range of highest, efficacious MIC ran from 0.015 mcg/ml (in immunocompetent and neutropenic rats with lobar pneumonia due to PSSP and PSRP) to 0.25 mcg/ml (in immunocompetent rats with pneumonia infected with PRSP). (b) (4)

HUMAN PHARMACOKINETICS

The PK of IV dalbavancin are well characterized in healthy subjects, special populations, and the intended patient population. Dalbavancin was well tolerated in all Phase 1 clinical studies. There were no dose-dependent or special population-dependent safety observations. No maximum tolerated dose was observed in any of the ascending dosage studies. The highest total dosage examined was a daily dosage regimen that administered a cumulative dosage of 1600 mg over a 7-day period (VER001-2). The highest single dose administered in a Phase 1 study was 1500 mg (DUR001-101, DUR001-102).

Absorption

In Study VER001-15, nine patients were administered 1000 mg of dalbavancin IV over 30 minutes. Mean peak plasma concentrations of dalbavancin were 285 (± 31) mg/L and were achieved immediately (0.75 hr) following the end of infusion. Dalbavancin was slowly eliminated with a terminal t1/2 of 15.5 days. Dalbavancin has a volume of distribution of approximately 13.8 (± 2.3) L and total drug CL of 0.0405 (± 0.0053) L/h. There were no measurable concentrations of OH-dalbavancin observed in plasma (below level of quantitation [BLQ] = 0.4 mg/L). The estimated fraction of drug excreted unchanged into urine was approximately 19% of the administered dose and the renal clearance (CLr_dal) was estimated as 0.0081 (± 0.0034) L/h. The estimated amount of OH-dalbavancin metabolite excreted in the urine was approximately 8% of the total dose and the renal clearance (CLr_OH-dal) was estimated as 0.0032 (± 0.0004) L/h. The estimated fraction of drug excreted unchanged into feces was approximately 20% of the administered dose. Mean dalbavancin concentrations in skin were above 30 mg/L through Day 7. The relative exposure of dalbavancin into skin (AUCskin/AUCplasma) was approximately 60%.

Distribution

The Cmax of dalbavancin is achieved immediately following the end of infusion. Dalbavancin distributes into a V_{SS} of 14 L. This is a distribution volume that is approximately 20% of body weight, and consistent with the assumption that the drug is distributed in the extracellular fluid. When adjusted by body weight, the VSS observed for humans (~ 0.2 L/kg) was similar to other species studied (mice, rats, rabbits, dogs, and pigs). Animal studies showed that dalbavancin was well distributed through the body.

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) is short and can be characterized by a $t_{1/2}$ of approximately 2.5 hours. An elimination phase (beta phase) follows that accounts for the majority of drug elimination ($t_{1/2}$ ~ 5 days). This elimination phase has been estimated with a t½ as long as a week in some studies. In patients, the predominant elimination rate was characterized by a $t_{1/2}$ of 8.5 days. With an

adequately long study, sensitive assay, and proper sampling, a terminal elimination phase can be observed with a $t_{1/2}$ of 16 days. The terminal elimination phase characterizes the lower concentrations (<10 mg/L) at later times in the concentration-time curve (>28 days). The variability of PK parameters both across and within studies and dose cohorts was low.

The protein binding measured in human plasma is 93%. Plasma protein binding is consistent across the wide therapeutic range studied (0.2 to 360 mg/L). The plasma protein binding was also studied in plasma samples from subjects with severe renal impairment and subjects with severe hepatic impairment. The protein binding in these populations was consistent with subjects with normal renal and hepatic function, and consistent within the wide range of concentrations studied.

Metabolism
Dalbavancin is not a substrate, inducer, or inhibitor of hepatic cytochrome P450 isoenzymes. No significant amounts of metabolite have been observed in human plasma, however a minor dalbavancin metabolite (OH-dalbavancin) has been observed in human urine. The presence of this minor metabolite is clinically insignificant because of the low to undetectable levels of OH-dalbavancin observed in plasma and because OH-dalbavancin is significantly less active than dalbavancin.

Small amounts of MAG are also observed in urine following administration of dalbavancin. Small amounts of MAG are present in the drug product, but may also be produced *in vivo* by biotransformation or degradation. MAG is also less active than dalbavancin and the presence of MAG is clinically insignificant.

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 (VER001-10). In humans, a total of 8% to 12% of the administered dose is excreted as OH-dalbavancin in urine (VER001-19, VER001-10). The metabolite has also been observed in the urine in rat and dog studies.

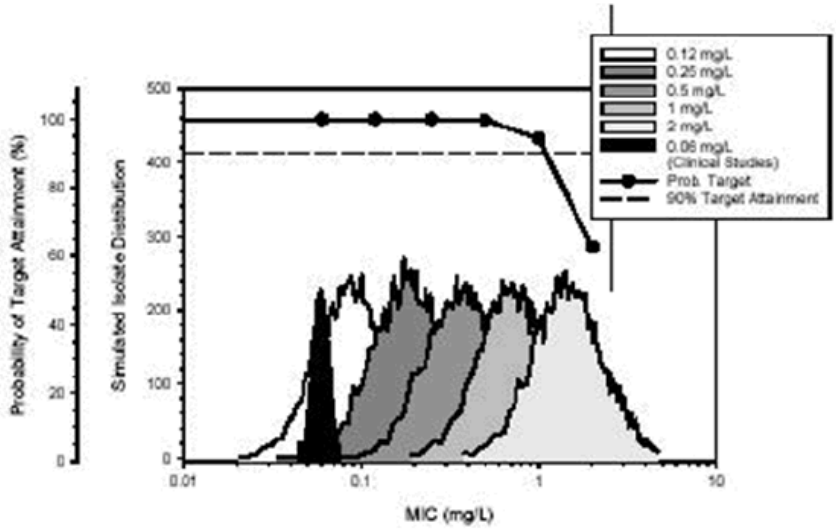
Animal studies have shown that dalbavancin is excreted into feces as intact drug, with only trace levels of metabolite found in feces. The excretion of dalbavancin into human feces was examined in VER001-19, and showed 20% of drug excreted into feces. Collectively, approximately 70% of the administered dose has been accounted for in collected excreta. The remaining 30% of the administered dose is also likely to be excreted in urine and feces, but may be eliminated at slower rates in the later points in the profile with concentrations in excreta that fall below the quantifiable limits of the assays.

Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis

The proposed dosage regimen for dalbavancin is 1000 mg on day one followed by 500 mg on day 8 (adjusted for renal function). Because of the extended disposition profile of dalbavancin this weekly regimen maintains therapeutically relevant concentrations and exposures of the drug throughout a 14-day treatment period. The degree of protein binding, based on MIC differences between broth and mouse serum and on direct binding studies in human plasma, is not identical in mouse and human (99.6% and 93% respectively).

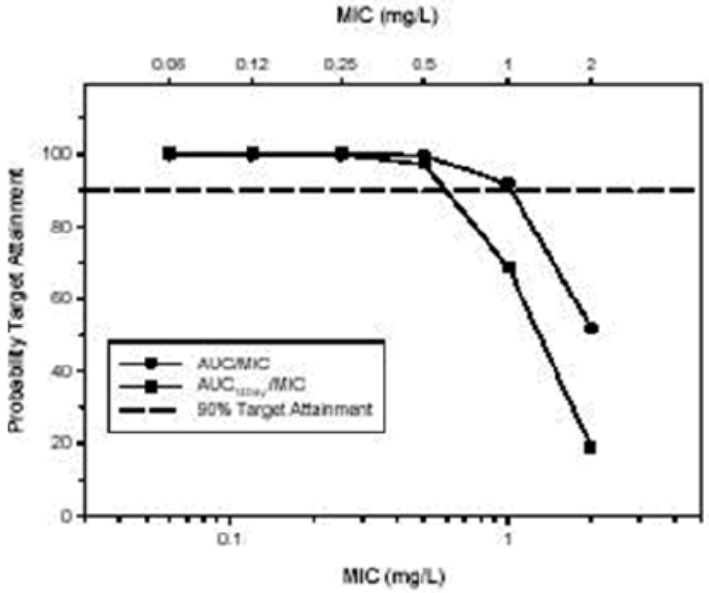
A Monte Carlo analysis has been performed, using both time-dependent and concentration dependent parameters. The time-dependent target was attainment of concentrations above the MIC through the entire 14-day treatment duration (t>MIC=100%). The concentration-dependent target was attainment of the free drug AUC/MIC ratio targets (1000 for *S. aureus* and 100 for *Streptococcus* spp.) determined from the neutropenic mouse study. The Monte Carlo analysis was performed using the MIC value distributions for *S. aureus* and *Streptococcus* spp. obtained in the three Phase 3 SSTI studies (VER001-8, VER001-9 and VER001-16). Higher MIC distributions were simulated and also included in the analysis. For the concentration-dependent PD parameter (AUC/MIC), simulations were performed calculating exposure through infinity (AUC_{∞}) and through 14 days (AUC_{14Day}). Based on these simulations, a target attainment of greater than 93% was obtained for a population of *S. aureus* with a MIC distribution where the MIC_{50}=0.5 µg/ml and the MIC_{90}=1 µg/ml (Figure 5 and Figure 6).

Figure 5. Simulated Target Attainment for Dalbavancin T>MIC against *S. aureus* Compared to MIC Distributions



Source: Figure 25, Microbiology section, this submission.

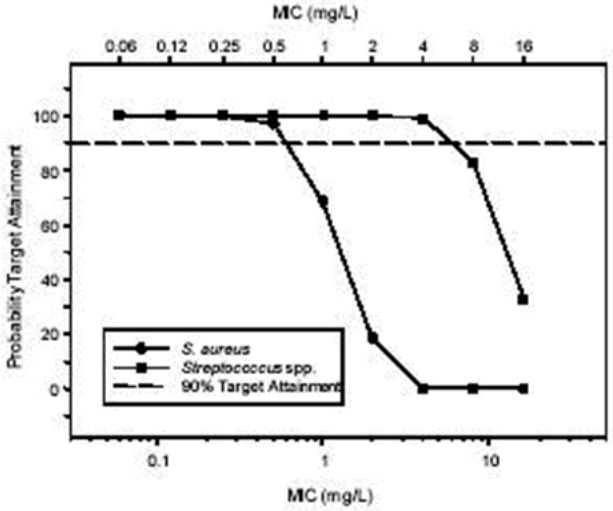
Figure 6. Comparison of Simulated Target Attainment for Dalbavancin AUC∞/MIC and AUC_{14Day}/MIC against *S. aureus*



Source: Figure 26, Microbiology section, this submission.

For streptococci, the target attainment rates previously determined were greater than 90% for all parameters (T>MIC, AUC_{∞}/MIC and $AUC_{14\ day}$/MIC) against populations with theoretical MICs above 0.25 µg/mL (Figure 7), supporting the rationale for identical susceptibility interpretive criteria for streptococci and *S. aureus*.

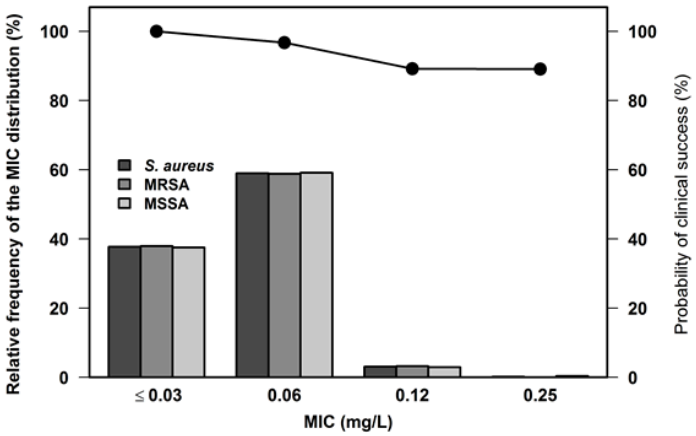
Figure 7. Comparison of Simulated Target Attainment (Dalbavancin AUC_{14Day}/MIC), *S. aureus* vs. *Streptococcus* spp.



Source: Figure 27, Microbiology section, this submission.

Recently, these PK/PD target attainment simulations have been updated using more recent MIC surveillance data and an enhanced population PK model based on study VER001-9. These PK exposures were then used in a PK/PD analysis to examine relationships between dalbavancin PK exposure and outcome at EOT. Monte Carlo simulation analyses were also conducted to assess PK/PD target attainment using both animal- and clinically-derived PK/PD targets for efficacy (Figure 8). The Applicant believes these analyses provide additional support for an *in vitro* susceptibility criterion of ≤ 0.25 µg/mL. The available data from this family of analyses suggest that the same criterion would be applicable to β-hemolytic and viridans streptococci.

Figure 8. Mean Percent Probabilities of Clinical Success by Dalbavancin MIC Overlaid over MIC Distributions for *S. aureus*, MRSA, and MSSA



Source: Figure 28, Microbiology section, this submission.

CLINICAL MICROBIOLOGY SUSCEPTIBILITY TEST METHODS

SUSCEPTIBILITY METHODOLOGIES

The reference method used to determine the *in vitro* activity of dalbavancin is the broth microdilution method of the Clinical and Laboratory Standards Institute (CLSI) (CLSI 2012a, CLSI 2013), which has been used in the majority of studies, including the characterization of clinical trial isolates. 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.

EFFECTS OF VARIATIONS IN TEST CONDITIONS

This section summarizes studies of the effects of variations in test conditions on the *in vitro* activity of dalbavancin. Initial testing of individual variables that might affect results was based on standard CLSI broth microdilution and agar dilution procedures (CLSI 2012a). Although standards of medium, inoculum size, etc. are stipulated, it is recognized that deviations from these methods can occur. Both CLSI and EUCAST methods include variables such as: inoculum size; incubation time and conditions; growth medium pH, composition, and cation concentrations.

Among the variables usually explored, only the addition of serum has a negative effect on the *in vitro* activity of dalbavancin, although in absolute terms MIC values and bactericidal concentrations of dalbavancin in the presence of 50% human serum are well below levels that are maintained in human plasma with the proposed dosage regimens.

However, it became clear that the major factor influencing dalbavancin broth microdilution MICs is the manner in which panels are prepared. This is related to solubility and the tendency of dalbavancin to adhere to plastic materials. More recently it has been shown that dalbavancin agar dilution MICs are higher than those determined by broth microdilution; this has implications for the accurate assessment of the susceptibility to dalbavancin of those organisms, such as anaerobes, that are normally tested on agar.

Agar Dilution MICs

It has been demonstrated that dalbavancin agar dilution MICs are generally higher than broth microdilution MICs both for anaerobes (as much as 64-fold higher) and aerobic organisms. In this study, the type of medium utilized had little effect.

In an earlier study, the effect of altering some of the standard conditions on the agar dilution MICs of dalbavancin was determined using CLSI agar dilution methodology with 22 Gram-

positive isolates (seven *S. aureus*, six CoNS, seven *Enterococcus* spp., two *Bacillus* spp., Jones 2001). Neither varying the pH over the range 6.0-8.0 nor varying the incubation atmosphere had an effect on agar dilution MICs. Similarly, MICs for only a few isolates were affected by increasing the inoculum size. Addition of blood to Mueller-Hinton agar, or use of other media (Brain Heart Infusion agar, *Brucella* agar) also had no effect on dalbavancin MICs. However, dalbavancin MICs were increased by up to 16-fold in chocolate agar.

Effect of Preparation Method on Broth Microdilution MICs

During validation studies of commercially prepared dry-form and frozen MIC panels, it was observed that dalbavancin MICs (unlike those of other agents) were on average 4-fold lower in the dry-form panels. This led to a series of experiments that culminated in standardization of the preparation of dalbavancin fresh or frozen panels to include solubilization and dilution in dimethylsulfoxide (DMSO) and addition of polysorbate-80 (P-80, Tween 80) to the diluent to produce a final concentration of 0.002% in the inoculated microtiter wells (CLSI 2013). It was demonstrated that dalbavancin (as measured by antimicrobial activity) was progressively lost from solution when it was gently shaken in a plastic receptacle (Rennie 2007).

Effect of Different Conditions on Broth Microdilution MICs and MBCs and Time-Kill Kinetics

Of note, some of the MIC/MBC determinations discussed here were conducted using fresh or frozen panels without addition of P-80, so the relative values (altered vs. standard condition) may be more relevant than the absolute MIC or MBC values.

Studies by (b) (4) examined the effect of variations from standardized conditions on dalbavancin MICs determined by broth microdilution (CLSI 2012a, CLSI 2013) using validated dry-form panels or freshly prepared panels containing a small amount of wetting agent (P-80). Various resistant strains and clinical isolates were tested and comparative data were generated for dalbavancin, teicoplanin and vancomycin. The base media were standard CAMHB for staphylococci and enterococci, and CAMHB + 2-5% lysed horse blood for streptococci.

Incubation time or temperature

There was no effect of incubation time (16 to 24 hours) or incubation atmosphere (5% CO_2 vs. air) on dalbavancin MICs (Report VER001-MI-001). Dalbavancin MICs for all 12 test strains were essentially the same under all of these conditions. Similarly, there was no effect of incubation temperature (30, 35, or 40°C) on dalbavancin MICs (Report (b) (4) 1548).

Medium composition

Doubling the standard Ca^{2+} concentration to 50 µg/mL (of interest because this is recommended for testing daptomycin, a possible comparator) had no effect on dalbavancin MICs (Report VER001-MI-001). Starting with unadjusted Mueller-Hinton broth, Ca^{2+} was varied

up to 100 µg/mL and Mg^{2+} up to 50 µg/mL (4 times normal) with no effect on dalbavancin MICs (b) (4)-1542-III).

When the pH of the medium was varied over the range of 5.0 to 8.0, dalbavancin modal MICs were within one doubling dilution of MICs at the standard pH of 7.2-7.4; however, the modal MIC increased 4-fold at pH 9.0 (Report VER001-MI-001).

Dalbavancin MICs were within one doubling dilution when strains were tested in three different broths: standard Mueller-Hinton, Tryptic Soy, or Brain Heart Infusion (Report (b) (4)-1547).

Inoculum size

At a rather high inoculum of 10^7 CFU/mL the modal dalbavancin MIC increased 4-fold, with higher multiples for some isolates, as compared with the standard 5×10^5 CFU/mL (Report VER001-MI-001). In comparison, modal MICs for vancomycin and teicoplanin increased by ≥ 8-fold at the higher inoculum. This may be related to the mechanism of action of the glycopeptides; in general, cell wall-active agents are more effective *in vitro* when bacteria are actively growing, and growth is limited when the starting inoculum is dense. Additionally, initial turbidity may be present at such a high inoculum density, which can confound the reading of endpoints.

Human or Animal Serum

The *in vitro* activity of dalbavancin is affected by the presence of human serum. However, a consistent observation in all studies has been that dalbavancin, at clinically relevant concentrations, has potent inhibitory and bactericidal activity *in vitro* in the presence of serum.

Although it is not possible to predict *in vivo* activity based on *in vitro* effects of serum, these effects may be relevant as dalbavancin is about 93% protein-bound in human plasma.

In one study, MICs for four of five staphylococcal isolates (*S. aureus* ATCC 29213, one MRSA and two MRSE strains), were increased with addition of 50% human serum by 4- to 32-fold; the MICs ranged from 0.03 to 1 µg/mL in the absence of serum and 0.5 to 4 µg/mL in the presence of serum. Interestingly, for a VISA strain that was tested (vancomycin and teicoplanin MICs of 8 µg/mL), the MIC of dalbavancin increased only 4-fold, from 1 to 4 µg/mL (Report VER001-MI-001). MICs in the presence of 50% serum were still well below sustainable dalbavancin serum levels for all of the strains.

The effect of human serum on the MBC of dalbavancin was also determined for the three *S. aureus* strains. The MBCs of dalbavancin for the reference strain and the MRSA strain, in the absence of serum, were 0.12 and 0.06 µg/mL, similar to the MICs for these strains. In the presence of 50% serum, the MBCs for these two strains were 8 and 4 µg/mL (respectively, four and two times the MICs determined under the same conditions). In the presence of 50% human

serum, the MBC for the VISA strain was also 8 µg/mL. These concentrations are below the minimum plasma levels observed over the entire treatment period in humans who received the proposed therapeutic regimen of dalbavancin.

The effect of animal serum supplementation on the *in vitro* activity of dalbavancin was examined in other studies (Candiani 1999, Report GE021-04, Report DAL02M-001). In the study by Candiani 1999, dalbavancin MICs for several methicillin-susceptible and -resistant staphylococci were increased by the addition of 50% bovine serum, but were never greater than 4 µg/mL against *S. aureus* isolates. The same publication describes animal infection experiments in which dalbavancin was highly efficacious against some of these same strains at lower and/or less frequent doses than vancomycin and teicoplanin.

Variable effects of 50% human serum supplement on dalbavancin MICs and MBCs vs. *S. aureus* strains are discussed in Report GE021-04. An effect of 50% human serum on dalbavancin MICs for *S. aureus* isolates (generally 64-fold increase) was also observed in another study (Report DAL02M-001). In a study of the effect of serum on the MBCs for a small number of strains (Report DAL02M-002), results were similar to those reported in Report VER001-MI-001 for two vancomycin-susceptible strains of *S. aureus*. MBCs were equivalent to the MICs, which were 0.25 µg/mL for both strains, and a serum effect of 16-fold was seen (i.e. MICs and MBCs of 4 µg/mL for both strains).

The conclusions from a number of time-kill experiments in the presence and absence of 50% human serum, were that dalbavancin is bactericidal, in the presence of serum, at concentrations that are maintained in humans throughout the dosing interval with the proposed dosage. In conjunction with a rabbit endocarditis experiment (Lefort 2004), it was observed that concentrations of dalbavancin (20 or 50 µg/mL) that are maintained for long periods in humans treated with the proposed dosage regimen were bactericidal against MRSA and VISA strains even in the presence of 90% rabbit serum.

Additionally, the results of time-kill experiments conducted in the absence of serum, using concentrations approximating free fractions (Report VER001-MI-011) are consistent with bactericidal action of dalbavancin against target organisms at free drug concentrations that are sustained in human plasma throughout the dosing interval.

Lung Surfactant

Some antibiotics such as daptomycin are adversely affected by lung surfactant, leading to inefficacy in pulmonary infections. Although dalbavancin is not at present targeted to this indication, the effect of Survanta® (Intratracheal Suspension Bovine Pulmonary Surfactant; Abbott Laboratories, Inc.) on the *in vitro* activity of dalbavancin was tested (Dunne 2012). CLSI methodology, with the appropriate dalbavancin- and daptomycin-specific supplementation of the medium was utilized. In contrast to the inhibitory effect seen with daptomycin (tested

against QC strains only), Survanta at 1% and 5% by volume had no effect (≤2-fold) on the MIC of dalbavancin for five strains each of *S. aureus* and *S. pneumoniae*.

MIC DETERMINATIONS IN CLINICAL AND NONCLINICAL STUDIES OF DALBAVANCIN

Most of the pathogens tested for susceptibility to dalbavancin in the various studies were Gram-positive aerobes, principally cocci. Although in some studies Gram-positive anaerobic organisms were tested utilizing the CLSI agar dilution method (CLSI 2012b), the MIC values for anaerobes should be considered approximate, as agar dilution methodology has not been standardized for dalbavancin.

Broth dilution methodology for Gram-positive aerobic pathogens

During standardization of broth microdilution methodology, discrepancies were noted between MIC values generated using commercially prepared dry-form microtiter trays (b) (4) and standard frozen panels, prepared by the same vendor, which produced higher and more variable MIC values. One parameter that was considered was loss of dalbavancin during preparation of frozen trays by sticking to plastic, because the dry-form trays have been developed to ensure complete solubilization and bioavailability of antimicrobial agents upon addition of inoculated broth.

Although affinity for plastic had not previously been shown to occur for glycopeptides, it was a phenomenon known to occur with some other antibiotic classes, such as the glycolipodepsipeptide ramoplanin. A series of experiments demonstrated that antimicrobial activity of dalbavancin was progressively lost from solution after brief exposure to plastic, and that a small amount of the wetting agent polysorbate-80 (P-80, also known as Tween80) would eliminate this problem (Rennie 2007). Because dalbavancin can adhere to plastic pipette tips, as well as to microtiter trays, fresh or frozen trays for broth microdilution testing of susceptibility to dalbavancin should be prepared with P-80 in the diluent and in the broth, so as to attain a final P-80 concentration in inoculated wells of 0.002% (vol/vol).

Details of the Method

(b) (4)

After appropriate testing, this method was adopted by CLSI and is included in document M100 (CLSI 2013). CLSI QC ranges for dalbavancin are based on the use of this method. (b) (4) . Dry-form microtiter panels, utilized in several surveillance and clinical studies of dalbavancin, do not require addition of P-80 and have been validated against the CLSI methodology (Jones 2004, Fritsche 2004, Holliday 2004). This is illustrated in Table 16; omission of P-80 results in a variable increase in the apparent MIC of dalbavancin (by about two dilutions on average) when using freshly prepared or frozen microtiter trays. Results with the dry-form panels without P-80 were the same as with the fresh or frozen panels with addition of P-80, and no further reduction in MIC was attained by adding P-80 to the dry-form panels.

Table 16. MIC Values of Dalbavancin Determined by Broth Microdilution Using Fresh, Frozen or Dry-Form Panels and Inocula Prepared with and without P-80

Isolate	Modal MIC (µg/mL)[a]					
	Fresh Panels		Frozen Panels[b]		Dry-Form Panels	
	- P-80	+ P-80[c]	- P-80	+ P-80[c]	- P-80	+ P-80[c]
MRSA 1	0.25	0.06	0.25	0.06	0.06	0.12
MRSA 2	0.25	0.06	0.25	0.06	0.06	0.12
ATCC 29213	0.25	0.06	0.25	0.03	0.06	0.12

a Each isolate was tested in triplicate.
b Frozen panels were held in the freezer for 7 days before use.
c Final P-80 concentration in the wells was (b) (4)
Source: Table 40, Microbiology Summary, this submission.

The CLSI broth microdilution method for determining dalbavancin MICs has now been standardized with P-80 in the diluent, instead of the inoculum, and with a final concentration of 0.002% (CLSI 2013).

For clinical studies DUR001-301 and DUR001-302, microtiter trays (standard frozen form) utilized by the central laboratory were prepared by (b) (4) (now part of (b) (4) . They were prepared by the current CLSI-approved method (CLSI 2013), which includes specific instructions for solubilizing and diluting dalbavancin in medium containing P-80 at a final concentration of a 0.002% in the wells.

Dry-form panels were used for MIC determinations in clinical study VER001-9, in the large SENTRY surveillance study and a number of the other nonclinical microbiology studies (Table 5, table not shown), as well as in other early clinical trials. Dry-form trays do not require addition of P-80 and have been validated against the CLSI method (Jones 2004, Fritsche 2004, Holliday 2004).

Development of Quality Control Limits for Frozen MIC Panel

A QC study for the broth microdilution MIC method for dalbavancin was conducted by JMI Laboratories (Report VER001-MI-006, Anderegg 2003) according to the CLSI M23 guidelines (CLSI 2008). A total of eight participants (seven laboratories in the US and one in Canada) contributed data to this investigation. Each site used four broth lots of each medium type and tested the QC strains daily for 10 days. Vancomycin was concurrently tested as a control agent; all 480 MIC results for vancomycin were within range.

On the basis of this study, the QC ranges listed in Table 17 were proposed and approved by CLSI.

Table 17. CLSI Approved Quality Control Ranges for Dalbavancin and Percent of MIC Values in Range

Organism	MIC Range (µg/mL)	Percent in Range*
E. faecalis ATCC29212	0.03 - 0.12	100
S. aureus ATCC 29213	0.03 - 0.12	100
Streptococcus pneumoniae ATCC 49619	0.008 - 0.03	99.7

* There were 320 MIC determinations for each organism (Anderegg 2003).
Source: Table 41, Microbiology Summary, this submission.

Validation of Dry-Form Microdilution MIC Panels

Dry-form microdilution panels were used to generate much of the surveillance data and other non-clinical data supporting the use of dalbavancin to treat abSSSI as well as early clinical trials of its efficacy in cSSSI and uSSSI. These panels were validated against frozen microdilution panels (Jones 2004). The protocol followed the validation recommendation published in CLSI document M23 (CLSI 2008) using organism groupings within the spectrum of dalbavancin activity: 65 isolates of *S. aureus* (42 methicillin-resistant), 36 CoNS (27 methicillin-resistant), 20 *S. pyogenes*, 20 *Streptococcus agalactiae*, 50 viridans group streptococci (24 penicillin non-susceptible), 100 *S. pneumoniae* (24 penicillin non-susceptible), and 101 *Enterococcus* spp. Additionally, 27 Gram-negative isolates, not within the spectrum of activity of dalbavancin, were tested.

Dalbavancin MIC values obtained with the reference frozen panels (CLSI 2012a) vs. commercial dry-form panels for the 402 Gram-positive and 27 Gram-negative isolates are compared in Table 18.

Table 18. Validation Experiments Comparing Dalbavancin MIC Values from Dry Form Panels with Those from Frozen Reference Panels

Organism Group (Number Tested)	Dry-Form MIC Variation in Log_2 Dilution, Number (%)				
	-2	-1	Same	+1	+2
S. pneumoniae (100)	0	5	86	9	0
Other streptococci (100)[a]	1	4	91	4	0
Staphylococci (101)[b]	0	2	72	26	1
Enterococci (101)[c]	0	0	51	50	0
Subtotal (402 Gram-positives)	1	11	300	89	1
Gram-negative organisms (27)[d]	0	0	27	0	0
Total (429)	1 (0.2)	11 (2.6)	327 (76.2)	89 (20.8)	1 (0.2)

a Includes 50 viridans group isolates (24 penicillin-non-susceptible), 20 *S. pyogenes*, 20 *S. agalactiae* and 10 from serogroups C, F and G.
b Includes 65 *S. aureus* (42 methicillin-resistant) and 36 CoNS (27 methicillin-resistant).
c Includes 61 *E. faecalis* (7 VRE), 30 *E. faecium* (14 VRE), 3 *E. casseliflavus*, 3 *E. gallinarum* (1 VRE), 2 *E. raffinosus* and one strain each of *E. hirae* (VRE) and *E. avium* (VRE).
d Includes isolates representing 14 species among *Enterobacteriaceae* and non-fermentative Gram-negative bacilli.
Source: Table 42, Microbiology Summary, this submission.

For Gram-positive strains, 99.5% of all dalbavancin MIC values from the dry-form panels were within ±1 log2 dilution step of results with the reference frozen panels. Identical dalbavancin MIC values were obtained in both tests for 74.6% of the Gram-positive isolates. Overall, the MIC values obtained with the dry-form reagents were slightly elevated compared with the reference method (CLSI 2013) for staphylococcal (26.7%) and enterococcal (49.5%) isolates.

> ***Reviewer's comments***: Dalbavancin MICs using dry form panels were identical to frozen reference panels 86%, 91%, 72% and 51% of the time for *S. pneumoniae*, other streptococci, staphylococci and enterococci, respectively. In other words, MICs using dry form panels varied by at least one dilution compared to frozen reference panels 14%, 9%, 28% and 49% of the time for *S. pneumoniae*, other streptococci, staphylococci and enterococci, respectively. Overall, Gram positive strains varied 25% of the time. In all cases, variation was by at least 9%.

For all Gram-negative organisms, MIC values were >32 µg/mL with both methods. Control vancomycin tests were performed concurrently and all MIC values were within CLSI QC limits.

Additionally, reproducibility testing utilized 10 Gram-positive organisms, including four QC strains recommended by the CLSI (CLSI 2012a, CLSI 2013). Each strain was tested on three occasions daily for three consecutive days. Analysis of the reproducibility of the dry-form panels within the same day showed 92.2% identical results. Similarly, between-day reproducibility showed 80.9% identical results, with all values within one two-fold dilution. Dalbavancin MIC values for the QC strains (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC

49619) were consistently and reproducibly at the mid-point of the proposed QC ranges (Anderegg 2003). Complete details of these experiments may be found in Jones 2004.

QUALITY CONTROL STUDIES

(b) (4) served as the central reference laboratory for the abSSSI studies DUR001-301 and DUR001-302. Concurrently with MIC determinations for study isolates, dalbavancin MIC values were determined for the CLSI QC strains. QC data are also available for a recent surveillance study of European isolates. Susceptibility data were considered valid only when the dalbavancin QC MIC values were in range. In the course of the studies *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).

(b) (4), acquired by (b) (4) was the central microbiology laboratory for study VER001-9, as well as for two earlier Phase 3 SSSI studies, and also conducted a surveillance study of staphylococci and streptococci from diverse geographic sources and with a variety of antibiotic resistances (Report VER001-MI-004). In all of these studies, concurrently with MIC determinations for study isolates, MIC values were determined for the CLSI QC strains. For all three test organisms (a total of more than 80 determinations), the modal MIC was in the center of the QC MIC range. There was only a single MIC value that was out of range; this was for *E. faecalis* ATCC 29212.

Studies conducted at JMI Laboratories included the extended SENTRY surveillance study. (b) (4) also served as the central microbiology laboratory for two Phase 2 efficacy studies (VER001-4 and VER001-5) and processed isolates from nasal swabs in a Phase 1 study (VER001-11). In all of these studies, concurrently with MIC determinations for study isolates, dalbavancin MIC values were determined for the CLSI QC strains. In more than 1,000 tests of *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 all values were within the CLSI MIC ranges and the modes (which included >50% of tests for each organism) were both 0.06 µg/mL, right in the middle of the QC ranges. Similar reproducibility was reported during other *in vitro* studies, with either frozen or dry-form microtiter panels.

MIC Ranges for QC Isolates during Clinical Trials and Surveys

(b) (4) performed the studies that included *in vitro* susceptibility testing on two non-clinical trial surveys of isolates worldwide. (b) (4) also conducted *in vitro* studies for the Phase two efficacy trials (VER001-4 and VER001-5), and process isolates from nasal swabs in a Phase I study.

(b) (4) conducted the *in vitro* study of MIC values for the Phase III efficacy studies (VER001-8, VER001-9, and VER001-16) and determination of MIC values of staphylococci and streptococci (VER1-MI-004) from the different geographic locations and with a variety of

antibiotic resistance profiles. In all these studies, the Applicant reported that MIC values for QC isolates were determined concurrently. The Table below (Table 19) summarizes the QC ranges obtained during the clinical trials and in performing the surveys of non-clinical trial isolates. In this summary report, it shows that all values were within CLSI (NCCLS) QC range established for dalbavancin.

Table 19. Quality control ranges obtained in the *in vitro* susceptibility testing of isolates recovered in clinical trials and worldwide surveys

QC Strain	MIC mcg/mL		
	Mode	Range	% in range
E. faecalis ATCC® 29212	0.06	0.03-0.06	100%
S. aureus ATCC ®29213	0.03	0.03-0.-06	100%
S. pneumoniae ®ATCC 49619	0.016	≤0.008-0.03	100%

Based on the report provided by the Applicant, it appears that the QC data for dalbavancin obtained during the clinical trials and surveys using the dry-format microtiter trays were in range and the results were acceptable.

Agar Based Methodology for Determination of Susceptibility to Dalbavancin

Standardization of the agar dilution method for dalbavancin and determination of the relative QC limits have not been completed, and this method is not recommended when other methods are available. Agar dilution methodology has been used to determine dalbavancin MICs for anaerobes and, in limited studies, for some bacteria that grow aerobically; however, comparative data suggest that dalbavancin MIC values determined in agar may be about 4-fold higher than those determined with validated broth microdilution methodology. A study comparing the Etest with broth and agar dilution concluded that MICs were 2-fold higher with agar dilution than with the other two methods (Fritsche 2006). In recent studies, higher MIC values in agar than in broth (generally more than 4-fold) were documented for Gram-positive aerobic cocci, Gram-positive anaerobes, and *N. gonorrhoeae*.

ETest

At present dalbavancin disks are not available and are not recommended for use in susceptibility testing. Technical issues preventing the correlation of inhibition zones with MIC values appear to include poor diffusion out of the disk and radially in the agar. Studies have been conducted by AB Biodisk (now BioMérieux) with the aim of developing an Etest for dalbavancin susceptibility testing. This method has been validated against the broth microdilution method of MIC determination (Fritsche 2006). Isolates tested (total 200) included *S. aureus*, CoNS, β-hemolytic streptococci, viridans streptococci, *S. pneumoniae* and

enterococci. The sample included methicillin-resistant staphylococci and VRE. MIC values determined by the Etest were within the CLSI QC range (established for broth microdilution) in multiple tests of the QC strains. Additionally, Etest MICs for the 200 clinical isolates were all within ±2 log2 dilution steps (92.5% within one dilution) of the broth microdilution MICs.

PROVISIONAL SUSCEPTIBILITY TESING INTERPRETIVE CRITERIA

Submission of a provisional susceptibility breakpoint plan prior to the NDA was identified as an action item at the End of Phase 2 meeting on 30 October 2002. At the meeting, the Sponsor was informed of the Agency's preference that susceptibility breakpoints for dalbavancin be proposed prior to Phase 3. Because of the difficulties in establishing breakpoints for dalbavancin, the Agency and the Sponsor agreed to continue discussion on this topic. The Agency encouraged the Sponsor to characterize dalbavancin PK/PD parameters. A provisional breakpoint was not established prior or during the Phase 3 clinical trials. Submission of a proposed susceptibility breakpoint plan prior to the NDA was identified as an action item. A proposed susceptibility breakpoint plan (but no provisional breakpoints) was submitted for review on 23 March 2004.

Because of the narrow range of dalbavancin MIC against SSSI target pathogens, primarily *S. aureus* and streptococcal species, a susceptibility threshold did not emerge from the analysis of the responses obtained in Phase II clinical studies. In addition, dalbavancin susceptibility disk methodology was not available for local clinical study sites to guide therapy hence; the susceptibility interpretive criteria for vancomycin were used by the Applicant during clinical trials to determine an isolates susceptibility to dalbavancin**.** Although encouraged to provide the Agency with a provisional breakpoint during the course of the clinical trials (IND review dated 10 May 2004), the Applicant, instead, submitted a plan to propose a susceptibility breakpoint for staphylococcus and streptococcal species.

CLINICAL EFFICACY

Background
The efficacy of dalbavancin for the targeted treatment indication of abSSSI and cSSTI was evaluated in three pivotal studies (DUR001-301, DUR001-302, and VER001-9). Each of these were randomized, double-blind (third party unblinded), multi-center studies. Patients with infections consistent with abSSSI or cSSTI, both defined as infections involving deeper soft tissue or requiring significant surgical intervention, were eligible for DUR001-301 and Study DUR001-302 or VER001-9, respectively. Additionally, three supportive studies (VER001-16, VER001-8, and VER001-5) evaluated the use of dalbavancin in SSTI subjects and one study (VER001-4) evaluated the use of dalbavancin in CRBSI subjects.

What follows are synopses of the three pivotal studies: DUR001-301, DUR001-302 and VER001-9.

SYNOPSIS OF STUDY VER001-9

Phase 3, Randomized, Double-Blind, Multi-Center Study to Evaluate the Safety and Efficacy of Dalbavancin Versus Linezolid in the Treatment of Complicated Skin and Soft Tissue Infections with Suspected or Confirmed Gram-Positive Bacterial Pathogens (2004)

This clinical study was a Phase 3 randomized, double-blind, multi-center study to evaluate the safety and efficacy of dalbavancin versus linezolid in the treatment of complicated skin and skin structure infections (cSSSI) with suspected or confirmed gram-positive bacterial pathogens. Sixty-five (65) centers in seven (7) countries enrolled or treated at least one patient participated in this study. Of the 873 enrolled patients, 718 were from the United States.

The primary objective of the study was to compare the efficacy and safety of dalbavancin in the treatment of adults with cSSSI to that of linezolid. The secondary objective was to compare the microbiological efficacy between treatment arms and to obtain dalbavancin pharmacokinetics and pharmacodynamic data in patients with this disease entity.

The study was conducted between 3 January 2003 and 21 May 2004. In this study, patients were randomized 2:1 (dalbavancin vs. linezolid). All patients initiated dalbavancin treatment intravenously on Day 1 (1000 mg) with an option for a second 500 mg dose on Day 8 for a total course of therapy of 7 or 14 days. Patients assigned to dalbavancin also received IV placebo q 8h after the first dalbavancin infusion until criteria for switching to oral placebo q 6 h were met. Patients assigned to linezolid received IV linezolid 600 mg q 12h with a possible switch to oral linezolid 600 mg q 12 h after at least 24 hr of parenteral therapy for a total course of 7 or 14 days therapy.

Cultures were obtained from the cSSSI site and from blood (if clinically warranted) at baseline for identification of Gram-positive pathogens. Cultures of the cSSSI site were repeated at each study visit, if clinically warranted, or if the patient was deemed a failure. Blood cultures were repeated until negative results were obtained only if positive at baseline.

The study population included patients with cSSSI defined as infection which met the following criteria:

- Suspected to be caused by only Gram-positive bacterial pathogens including MRSA
- Involved deeper soft tissue as major abscesses, burns on $\leq$ 20% body surface area, traumatic wound infection, extremities with ulcerating cellulites and surgical wound infections.

Excluded were patients with known or suspected osteomyelitis or septic arthritis, those with infections expected to need more than two surgical interventions during the study, and those with concomitant conditions requiring antimicrobial therapy that would interfere with the evaluability of the condition under study were excluded from participation.

The primary efficacy endpoint was clinical response at the test-of-cure (TOC) assessment in the clinically evaluable population. Secondary efficacy endpoints included clinical response at TOC and EOT in the intent-to-treat (ITT), microbiological ITT and microbiological evaluable population among others.

SYNOPSIS OF STUDY DUR001-301

A Phase 3, Randomized, Double-blind, Double-dummy Study to Compare the efficacy and Safety of Dalbavancin to a Comparator Regimen (Vancomycin and Linezolid) for the Treatment of Acute Bacterial Skin and Skin Structure Infections (2012)

Study Sites: This was a multisite study in 7 countries and 54 sites including 27 sites in the United States of America.

Objectives:
The ***primary objective*** of this study was to compare the early clinical efficacy (after 48 to 72 hours of therapy) of dalbavancin to the comparator regimen (vancomycin with the option to switch to oral linezolid [vancomycin/linezolid]) for the treatment of patients with a suspected or proven gram-positive acute bacterial skin and skin structure infections (abSSSI).

The ***secondary objectives*** of this study were:

- To compare the clinical efficacy at the end-of-treatment visit (EOT) of dalbavancin to the comparator regimen.

- To compare the per-patient microbiological efficacy of dalbavancin to the comparator regimen.
- To compare clinical efficacy by individual pathogens in the two treatment groups.
- To compare pathogen eradication rates for individual pathogens in the two treatment groups.
- To compare the safety and tolerability of dalbavancin to that of the comparator regimen.

Additional objectives of this study were to compare the clinical efficacy of dalbavancin to the comparator regimen for the treatment of patients with suspected or proven Gram-positive abSSSI at the short-term follow-up visit (SFU) and the long-term follow-up visit (LFU).

This was a phase 3, randomized, double-blind, double-dummy study to compare the early clinical efficacy (48 to 72 hours of therapy) of dalbavancin to a comparator regimen (vancomycin with the option to switch to oral linezolid [vancomycin/linezolid]) for the treatment of subjects with suspected or proven Gram-positive abSSSI. Subjects were randomized in a 1:1 ratio to receive either IV dalbavancin (1000 mg on Day 1, 500 mg on Day 8) or IV vancomycin (1000 mg or 15 mg/kg [depending on the study site standard of care]) every 12 hours for 10 to 14 days, with possible switch after 72 hours to oral placebo in the dalbavancin group (the patient still received the planned dalbavancin infusion on Day 8) or linezolid (600 mg every 12 hours) in the vancomycin/linezolid group. Placebo was given on Days 1 and 8 (IV infusion) or every 12 hours (IV infusion or oral) to match the dalbavancin or comparator dosing regimen, respectively. Subjects with creatinine clearance values of <30 mL/min not receiving regular hemodialysis or peritoneal dialysis received either reduced doses of dalbavancin (750 mg on Day 1 and 375 mg on Day 8) or had their vancomycin dosages and intervals adjusted by an unblinded pharmacist as necessary, based on local standard of care, renal function, and vancomycin levels.

Baseline assessments were performed within 24 hours before the first dose. On Day 1, subject IV treatment was initiated and temperature was recorded. Efficacy assessments were made on Days 2, 3, 4, 8, and 14 or 15. An EOT assessment took place on Days 14 or 15, or within three days following premature discontinuation of treatment. A short-term follow-up visit (SFU) was planned for Day 28 and a final LFU at Day 70.

Diagnosis and Main Criteria for Inclusion:
Patients were male or female, aged 18 to 85 years, 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 two local signs of abSSSI (purulent drainage/discharge, fluctuance, heat/localized warmth, tenderness to palpation, and swelling/induration), at least one systemic sign of infection (an elevated body temperature ≥38°C/100.4°F as measured by the patient/caregiver or investigator within 24 hours of Baseline; white blood cell [WBC] count >12,000 cells/mm^3; a manually performed WBC differential count

with ≥ 10% band forms, regardless of peripheral WBC count), and infection severity requiring a minimum of three days of IV therapy.

Criteria for Efficacy Evaluation:
Efficacy assessments included clinical assessments (evidence of systemic inflammation and infection site assessment) and microbiology (blood cultures and infection site specimen collection).

SYNOPSIS OF STUDY DUR001-302

A Phase 3, Randomized, Double-blind, Double-dummy Study to Compare the efficacy and Safety of Dalbavancin to a Comparator Regimen (Vancomycin and Linezolid) for the Treatment of Acute Bacterial Skin and Skin Structure Infections (2012)

Study site(s): This was a multisite study. Patients from 144 sites in 14 countries were screened and patients from 86 sites in 14 countries were enrolled.

Objectives:
The ***primary objective*** of this study was to compare the early clinical efficacy after 48 to 72 hours of therapy of dalbavancin to the comparator regimen (vancomycin with the option to switch to oral linezolid [vancomycin/linezolid]) for the treatment of patients with a suspected or proven gram-positive acute bacterial skin and skin structure infections (abSSSI).

The ***secondary objectives*** of this study were:
• To compare the clinical efficacy at the end-of-treatment visit (EOT) of dalbavancin to the comparator regimen.
• To compare the per-patient microbiological efficacy of dalbavancin to the comparator regimen.
• To compare clinical efficacy by individual pathogens in the two treatment groups.
• To compare pathogen eradication rates for individual pathogens in the two treatment groups.
• To compare the safety and tolerability of dalbavancin to that of the comparator regimen.

Additional objectives of this study were to compare the clinical efficacy of dalbavancin to the comparator regimen for the treatment of patients with suspected or proven Gram-positive abSSSI at the short-term follow-up visit (SFU) and the long-term follow-up visit (LFU).

Study Plan:
This was a phase 3, randomized, double-blind, double-dummy study to compare the early clinical efficacy (48 to 72 hours of therapy) of dalbavancin to a comparator regimen (vancomycin with the option to switch to oral linezolid [vancomycin/linezolid]) for the treatment of subjects with suspected or proven Gram-positive abSSSI. Subjects were

randomized in a 1:1 ratio to receive either IV dalbavancin (1000 mg on Day 1, 500 mg on Day 8) or IV vancomycin (1000 mg or 15 mg/kg [depending on the study site standard of care]) every 12 hours for 10 to 14 days, with possible switch after 72 hours to oral placebo in the dalbavancin group (the patient still received the planned dalbavancin infusion on Day 8) or oral linezolid (600 mg every 12 hours) in the vancomycin/linezolid group. Placebo was given on Days 1 and 8 (IV infusion) or every 12 hours (IV infusion or oral) to match the dalbavancin or comparator dosing regimen, respectively. Subjects with creatinine clearance values of <30 mL/min not receiving regular hemodialysis or peritoneal dialysis received either reduced doses of dalbavancin (750 mg on Day 1 and 375 mg on Day 8) or had their vancomycin dosages and intervals adjusted by an unblinded pharmacist as necessary, based on local standard of care, renal function, and vancomycin levels.

Baseline assessments were performed within 24 hours before the first dose. On Day 1, subject IV treatment was initiated and temperature was recorded. Efficacy assessments were made on Days 2, 3, 4, 8, and 14 or 15. An EOT assessment took place on Days 14 or 15, or within three days following premature discontinuation of treatment. An SFU was planned for Day 28 and a final LFU at Day 70.

Diagnosis and main criteria for inclusion:
Patients were male or female, aged 18 to 85 years, with a known or suspected Gram-positive abSSSI (major cutaneous abscess, surgical site or traumatic wound infection, or cellulitis) accompanied by at least 75 cm^2 erythema, at least two signs of abSSSI (purulent drainage/ discharge, fluctuance, heat/localized warmth, tenderness to palpation, and swelling/ induration), at least one systemic sign of infection (an elevated body temperature ≥38°C/ 100.4°F as measured by the patient/caregiver or investigator within 24 hours of Baseline; white blood cell (WBC) count >12,000 cells/mm^3; a manually performed white blood differential count with ≥ 10% band forms, regardless of peripheral WBC count), and infection severity requiring a minimum of three days of IV therapy.

Criteria for efficacy evaluation:
Efficacy assessments included clinical assessments (evidence of systemic inflammation and infection site assessment) and microbiology (blood cultures and infection site specimen collection).

MICROBIOLOGY METHODS

Gram Staining of Material from the Site of Infection:
One slide for Gram stain is to be prepared from each specimen obtained from the infected site. The slide is to be stained and read by the local laboratory and then sent to the central laboratory for rereading and confirmation. A review of each slide should note the presence or absence of organisms and as well as squamous and polymorphonuclear cells.

A Gram stain of material obtained from the site of a skin infection provides supportive information that may help interpret the results of a culture obtained from that site. Every effort should be made, prior to culture, to perform a Gram stain of the material obtained from a needle aspiration, deep swab performed under sterile conditions, or from biopsy material. A supportive Gram stain documents the presence of the organism of interest as well as local inflammation as defined by the presence of inflammatory cells such as polymorphonuclear leukocytes. Note that a positive culture for a targeted pathogen without a supporting Gram stain could still be considered microbiologic evidence of infection and a Gram stain identifying a target organism and inflammation may not necessarily provide evidence of infection without additional positive results obtained through culture.

Infection Site Specimen Collection

Specimens should be collected at Baseline and as needed. Infection site specimen collection is described in Table 20.

Table 20. Acceptable Methods for Infection Specimen Collection

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 taken
Abscess	• Purulent fluid • Biopsy material	• Aseptic aspiration of purulent material/fluid. • Biopsy material obtained from I&D under sterile conditions
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
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

* 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 iodophor (e.g. 5% povidone-iodine); an alcohol-containing product (e.g. 70% ethyl alcohol, 70% isopropyl alcohol); chlorhexidine gluconate; a combination product (e.g. 5% povidone iodine solution in 70% ethanol; or, > 0.5% chlorhexidine with alcohol).

Blood Cultures:
At Baseline/Day 1, before the administration of antibiotic therapy, two sets of blood cultures including aerobic and anaerobic, will be drawn at least five minutes apart. Samples should be obtained from different anatomical sites and not through an existing intravascular line. If the baseline culture(s) is/are positive for any Gram-positive pathogen, blood cultures should be repeated 48 to 72 hours after treatment initiation or as needed, and, if still positive for that same pathogen, repeated again 48 hours later. If cultures are positive for the same pathogen on three consecutive sampling dates, the patient should be withdrawn from the study. Blood cultures should be obtained at the EOT visit if the baseline culture(s) is/are positive for any pathogen.

Once an organism has been isolated and identified, the local laboratory must send a viable isolate to the central laboratory for confirmation of identification and susceptibility testing.

Culture Methods:
Culture media:
Staphylococcus species – Blood Agar Plate
Streptococcus species – Blood Agar Plate, with optochin disc for alpha strep a
Gram negative species – MacConkey and Blood Agar Plate
Anaerobic species – Blood Agar Plate and a Brucella plate
Incubation:
Aerobic species – 35°C incubator except for *Streptococcus* species, which are incubated in CO_2
Anaerobic species – Blood Agar Plate incubated aerobically at 35°C; and Brucella Plate in anaerobic bag/jar at 35°C

Organism Identification Methods:
Organism identification is performed using a Bruker MALDI-TOF instrument (MALDI = matrix assisted laser desorption ionization; TOF = time-of-flight mass spectrometry) and followed up with biochemical tests if needed per (b) (4) Standard Operating Procedure (SOP) 1-P-PR-PRO-9002482.

Antimicrobials Tested:
Dalbavancin, Vancomycin, Oxacillin, Telavancin, Teicoplanin, Erythromycin, Clindamycin, Tetracycline, Levofloxacin, Daptomycin, Linezolid, Trimethoprim/Sulfamethoxazole and Penicillin

Method of Saving Isolates:
For each isolate, an 18-48 hour pure culture is used to inoculate cryovials prefilled with Brucella Broth with 20% glycerol. The inoculated cryovials are then stored at -80°C.

Method of Tracking Specimens and Isolates Sent to the Central Laboratory:
The storage and retrieval of isolates is tracked using a computerized system known as InVitro LIMS (LIMS = laboratory information management system). Using this system, all isolates received from clinical sites or isolated from specimens received from clinical sites are given an isolate identification number, and each isolate identification number is matched with a storage location in a specific (b) (4) freezer.

Culture and Susceptibility Testing
All clinically significant Gram-positive pathogens were tested locally for vancomycin susceptibility, as appropriate. The central laboratory will test all Gram-positive isolates for both vancomycin and dalbavancin susceptibilities. *Staphylococcus aureus* was also tested for oxacillin susceptibility as a marker for methicillin resistance by both the central and local laboratories. All clinically significant Gram-negative isolates will be tested for aztreonam and gentamicin susceptibility.

The local laboratory retained all isolates until the end of the study, if possible, or until confirmation of a viable organism is received from the central laboratory. Back-up cultures were requested when the central laboratory did not receive a viable culture, or recovers an organism different from the one recorded by the local laboratory.

Organisms considered as pathogens
The following organisms were always considered a pathogen when isolated from an acceptable abSSSI specimen:

Monomicrobial infections caused by:

- *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

Polymicrobial infection caused by:

- any combination of *S. aureus*, Group A, B or C β-hemolytic streptococci, *Streptococcus anginosus-milleri* Group, *E. faecalis, E. faecium*, and Gram positive anaerobes

Even if the organism was isolated from an acceptable abSSSI specimen, the following organisms were never a pathogen:

- *S. saprophyticus*
- Corynebacterium spp.
- *S. epidermidis*
- Bacillus *spp.*
- Diphtheroids
- *Micrococcus* spp.
- *Lactobacillus* spp.
- *Candida* spp., *Aspergillus* spp., or other fungi

All isolates not defined above were assessed on a case-by-case basis via manual review by the Sponsor. If needed, patient clinical (e.g., type of infection, type of specimen, patient underlying conditions, etc.) and microbiological information (e.g., Gram stain) were used to assist in determining if the isolate is a pathogen. All organisms isolated from a blood culture and all Gram-negative organisms were reviewed by the Sponsor to determine if the organism is a pathogen.

Based on the results of *in vitro* testing, animal studies, PK/PD modeling, surveillance programs and clinical trial data, specifically study VER001-09, a provisional breakpoint for susceptibility of dalbavancin to Gram positive organisms, including methicillin sensitive and methicillin resistant *S. aureus*, is ≤ 0.25 μg/ml. Disc diffusion interpretive criteria are not available for dalbavancin. A detailed description of the relevant microbiology data is available in the investigator brochure.

In the phase 3 SSTI studies, the same reference laboratory was used for the definitive identification of pathogens, and the same panel of antibacterials was tested, using Clinical Laboratory and Standards Institute (CLSI, formerly National Committee for Clinical Laboratory Standards) methodology.

COMBINED CLINICAL OUTCOMES BY KEY TARGET PATHOGEN

Various responses are compared for the pooled abSSSI data set in Table 21. These include early response parameters and clinical status of success at EOT, which were specific to the DISCOVER program, for DUR001-301 + DUR001-302. Investigator assessment of response at EOT, which was an end point in all three studies, is presented for the pooled DISCOVER studies and also for these data pooled with the VER001-9 reanalysis subset.

At the early time point (48-72 hours) the success rate in DUR001-301 + DUR001-302, as measured by a >20% reduction in lesion size, an objective measurement, was generally higher

than for clinical response, particularly in the dalbavancin treatment arm. At EOT, response rates were >90% for most pathogens in both treatment arms. Due to the smaller sample sizes, the response rates for *S. agalactiae*, *S. dysgalactiae* and *S. anginosus* group streptococci were more variable.

Table 21. Successful Clinical Outcomes by Key Target Pathogen in Patients with Monomicrobial Infection

	48-72 Hours [1] (microITT)				End of Treatment [1] (ME)				End of Treatment [2] (ME)	
	Early Response		>20% Lesion Reduction		Clinical Status (ME)		Investigator Assessment		Investigator Assessment	
Baseline Pathogen	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator	Dalbavancin	Comparator[3]
S. aureus (All)	172/208 (82.7)	169/196 (86.2)	196/208 (94 2)	182/196 (92.9)	173/191 (90.6)	166/177 (93.8)	176/191 (92 1)	166/167 (93.8)	344/377 (91.2)	261/283 (92.2)
MRSA	66/82 (80.5)	47/57 (82.5)	75/82 (91.5)	50/57 (87.7)	66/74 (89.2)	48/50 (96.0)	67/74 (90.5)	48/50 (96.0)	167/184 (90.8)	99/109 (90.8)
MSSA	106/126 (84.1)	121/138 (87.7)	121/126 (96.0)	131/138 (94.9)	107/117 (91.5)	117/126 (92.9)	109/117 (93.2)	117/126 (92.9)	177/193 (91.7)	161/173 (93.1)
S.pyogenes	16/19 (84.2)	8/14 (57.1)	17/19 (89.5)	10/14 (71.4)	18/19 (94.7)	11/13 (84.6)	18/19 (94.7)	12/13 (92 3)	24/27 (88.9)	15/16 (93.8)
S.agalactiae	4/7 (57.1)	2/3 (66.7)	5/7 (71.4)	2/3 (66.7)	6/7 (85.7)	1/2 (50.0)	6/7 (85.7)	1/2 (50.0)	11/12 (91.7)	4/6 (66.7)
S.dysgalactiae	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	4/4 (100)	2/2 (100)
S.anginosus group	6/9 (66.7)	9/9 (100)	8/9 (88.9)	9/9 (100)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)
S.anginosus	1/2 (50.0)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
S.constellatus	3/5 (60.0)	6/6 (100)	4/5 (80.0)	6/6 (100)	5/5 (100)	5/6 (83.3)	5/5 (100)	5/6 (83.3)	5/5 (100)	5/6 (83.3)
S.intermedius	2/2 (100)	1/1 (100)	2/2 (100)	1/1 (100)	1/2 (50.0)	1/1 (100)	1/2 (50)	1/1 (100)	1/2 (50)	1/1 (100)

Responses are success/total (%).
1 Includes patients from DUR001-301 and DUR001-302
2 Includes patients from DUR001-301, DUR001-302 and reanalysis subset of VER001-9.
3 Vancomycin/Linezolid in studies DUR001-302 and DUR001-302; Linezolid in VER001-9.
Source: Table 63, Microbiology Summary, this submission.

CORRELATION OF *IN VITRO* SUSCEPTIBILITY AND CLINICAL OUTCOME

The clinical efficacy of dalbavancin was also not related to MICs for baseline isolates from any species. This is illustrated by the clinical status of success at EOT and the investigator's assessment of clinical outcome at EOT as a function of baseline MIC in patients with a single baseline pathogen. Table 22 shows the clinical status of success at EOT by baseline MIC for key pathogens from the pooled DUR001-301 and DUR001-302 studies.

Table 22. Clinical Status of Success at EOT by Dalbavancin MIC for Key Pathogens: Patients with a Single Gram-Positive Baseline Pathogen, Dalbavancin Arms (Studies DUR001-301 and DUR001-302)

ME Population			MITT Population		
MIC (µg/mL)a	No. Isolates	Clinical Success Rate (%)	MIC (µg/mL)a	No. Isolates	Clinical Success Rate (%)
S. aureus	N=189		*S. aureus*	N=204	
0.015	4	100	0.015	4	100
0.03	66	86.4	0.03	69	84.1
0.06	117	91.5	0.06	127	88.2
0.12	1	100	0.12	3	100
0.25	1	100	0.25	1	100
MRSA	N=71		MRSA	N=78	
0.03	36	88.9	0.03	38	86.8
0.06	34	94.1	0.06	38	89.5
0.12	0	0	0.12	1	100
0.25	1	100	0.25	1	100
S. pyogenes	N=20		*S. pyogenes*	N=20	
0.004	5	100	0.004	5	100
0.008	4	100	0.008	4	100
0.015	7	100	0.015	7	100
0.03	2	100	0.03	2	100
0.06	1	100	0.06	1	100
0.12	1	100	0.12	1	100
S. agalactiae	N=8		*S. agalactiae*	N=8	
≤0.001	1	100	≤0.001	1	100
0.008	2	0	0.008	2	0
0.015	1	100	0.015	1	100
0.03	4	75	0.03	3	75
S. anginosus Group	N=9		*S. anginosus* Group	N=9	
0.002	1	100	0.002	1	100
0.004	1	100	0.004	1	100
0.008	3	100	0.008	3	100
0.015	4	100	0.015	4	100

Source: Table 96, Microbiology section, this submission.

BREAKPOINT DISCUSSION

The Applicant requests a dalbavancin susceptibility breakpoint of ≤ 0.25 µg/mL for *S. aureus* based primarily on the following:

• A cut-off of ≤ 0.25 µg/mL appears to be justified on the basis of the natural epidemiological distribution of dalbavancin MICs. Dalbavancin MIC frequency distributions are unimodal for a given pathogen. The MIC90 of dalbavancin overall and for *S. aureus* has consistently been 0.06 µg/mL over time. Although the ≤ 0.25 µg/ml breakpoint would exclude isolates with dalbavancin MIC of 0.5 µg/ml, such isolates were only rarely encountered during eleven years of *in vitro* epidemiologic surveillance and no clinical trial isolate had a dalbavancin MIC >0.25 µg/mL.
• A PK/PD analysis based on the mouse thigh infection model and on clinical trial data supports a susceptibility breakpoint of at least 0.25 µg/mL.
• Dalbavancin exhibited clinical efficacy comparable to approved and common standard of care comparator agents.
• A susceptibility breakpoint of ≤ 0.25 µg/ml would minimize the likelihood that diagnostic testing will inadvertently declare a susceptible organism to be non-susceptible, a potentially important consideration for a new antibacterial agent.

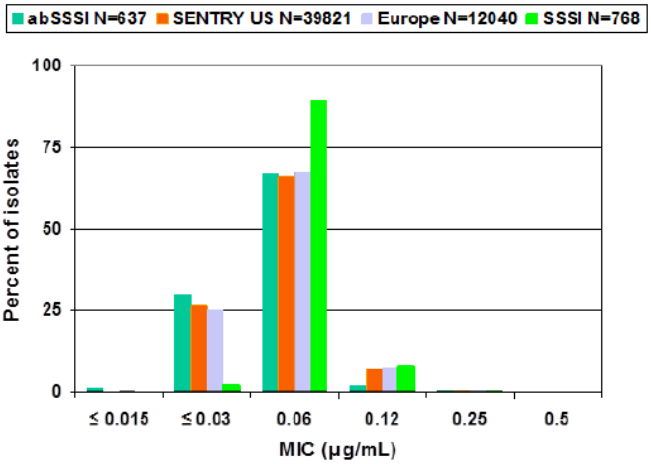
The Applicant requests the same susceptibility interpretive criterion, ≤ 0.25 µg/mL, for *S. pyogenes, S. agalactiae* and *S. anginosus* group that will be in the abSSSI indication.
• Although the MIC90 of dalbavancin for streptococcal species is usually lower (generally by one dilution step) than for *S. aureus*, the highest MIC values encountered were 0.25 µg/mL. There are no PK/PD or efficacy reasons to choose a different susceptibility breakpoint.
• There was clinical efficacy against pathogens with dalbavancin MICs of ≤ 0.002 to 0.12 µg/mL.

DALBAVANCIN MIC FREQUENCY DISTRIBUTIONS

MIC Distributions for *S. aureus*

Figure 9 shows the dalbavancin MIC distributions for the baseline isolates from the abSSSI trials and the surveillance studies.

Figure 9. Dalbavancin MIC Distributions: *S. aureus* from Clinical Trial (abSSSI and SSSI Baseline Isolates) and Surveillance Studies



Source: Figure 20, Microbiology section, this submission.

Reviewer's comments: The surveillance data consisting of more than 60,000 *S. aureus* isolates from the US and European surveillance data for 2002-2012 are consistent with the data from the four cSSSI and uSSSI studies. This is not surprising, as the MIC distributions for surveillance isolates in the SENTRY study have not varied from 2002 through 2012. The MIC values are distributed in a unimodal manner (0.06 µg/mL), and range from ≤ 0.015 to 0.25 µg/L in the clinical studies and ≤ 0.03 to 0.5 µg/mL in the SENTRY study.

For *S. aureus* the MIC90 of dalbavancin in both clinical and surveillance studies are 0.06 µg/mL. In the surveillance studies, 7.2% of the total isolates and in the clinical trials, only one isolate (ME population) had a MIC=0.12 µg/mL. There was only one isolate of 189 total isolates in the clinical trials and only 154 isolates of 39,824 (0.4%) in the surveillance studies in the US at MIC 0.25 µg/ml. There were even a smaller number of isolates at 0.5 µg/mL. There were no clinical isolates and only three isolates (< 0.1%) in the surveillance studies in the US with a MIC of 0.5 µg/ml.

Because the lowest concentration of dalbavancin reported in the SENTRY data is 0.03 µg/mL, this distribution appears truncated on the lower end; however it is clear that the MIC distributions are superimposable and consistent over time for both clinical trial and surveillance isolates. Dalbavancin MIC distributions for isolates from both clinical trials and surveillance studies were the same for the MRSA subsets as for all *S. aureus* (Figure 10, Microbiology section, thus submission, data not shown).

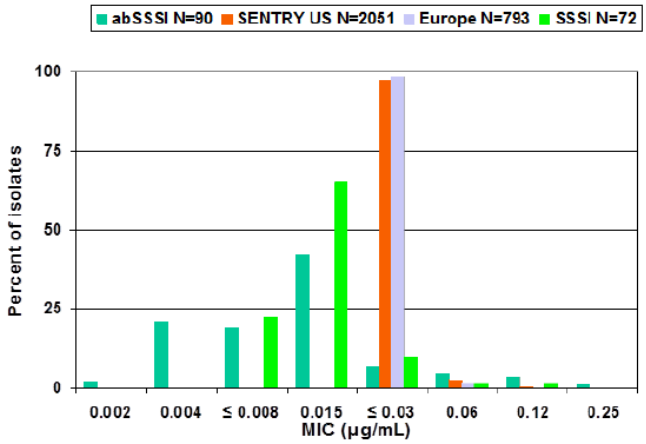
Conclusion: Based on the surveillance and clinical trial data, a susceptibility breakpoint of 0.06 µg/mL for *S. aureus* would be appropriate. A susceptibility breakpoint of 0.25µg/mL for *S. aureus* would be inappropriate as there is so little clinical experience and so few surveillance isolates with this MIC.

MIC Distributions for *Streptococcus* spp.

S. pyogenes

Figure 11 shows the dalbavancin MIC distributions for *S. pyogenes* abSSSI surveillance isolates from the U.S. (2002-2012) and Europe (2006-2009 SENTRY, Jones 2011a; 2011-2012, Deane 2012) as compared with results from the cSSSI and uSSSI clinical trials.

Figure 11. Dalbavancin MIC Distributions: *S. pyogenes* from Clinical Trial (abSSSI and SSSI Baseline Isolates) and Surveillance Studies



Source: Figure 22, Microbiology section, this submission.

Reviewer's comments: The US surveillance data consisted of more than 2,000 *S. pyogenes* isolates from the US for 2002-2012. The MIC distributions for surveillance isolates in the SENTRY study have not varied from 2002 through 2012. There is some skewing of the surveillance data, as 0.03 µg/mL was the lowest concentration of dalbavancin tested in that study. The MIC values are distributed in a unimodal manner in both the surveillance studies (≤ 0.03 µg/mL) and the clinical studies (0.015 µg/mL); the MICs ranged from ≤ 0.03 to 0.12 µg/mL in the SENTRY study and 0.004 to 0.12 µg/L in the clinical studies.

For *S. pyogenes* the MIC90 of dalbavancin in both clinical and surveillance studies is ≤ 0.03 µg/mL. There were only one isolate of 20 total isolates in the clinical trials and only 47 isolates of 2051 (2.3%) in the surveillance studies in the US with a MIC= 0.06 µg/ml. There were only one isolate of 20 total isolates in the clinical trials and only five isolates of 2051 (0.2%) in the surveillance studies in the US with a MIC= 0.12 µg/ml. There were no clinical isolates or surveillance isolates with a MIC ≥ 0.25 µg/ml.

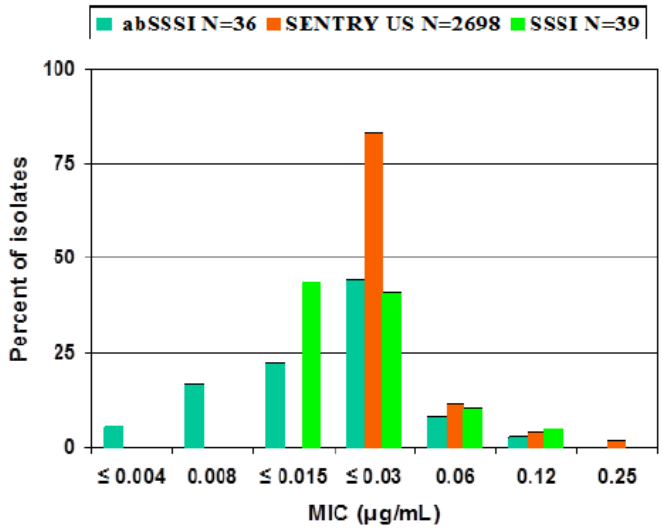
Conclusion: Based on the surveillance and clinical trial data, a susceptibility breakpoint of 0.06 µg/mL for *S. pyogenes* would be appropriate. A susceptibility breakpoint of 0.25µg/mL for *S. pyogenes* would be inappropriate as there is so little clinical experience and so few surveillance isolates with this MIC.

S. agalactiae

Figure 12 compares baseline clinical isolates of *S. agalactiae* from the abSSSI studies, the

four SSSI studies and U.S. surveillance data. There is some skewing of the surveillance data, as 0.03 µg/mL was the lowest concentration of dalbavancin tested in that study.

Figure 12. Dalbavancin MIC Distributions: *S. agalactiae* from Clinical Trial (abSSSI and SSSI Baseline Isolates) and Surveillance Studies



Source: Figure 23, Microbiology section, this submission.

Reviewer's comments: The US surveillance data consisted of 2700 *S. agalactiae* isolates from the US for 2002-2012. The MIC distributions for surveillance isolates in the SENTRY study have not varied from 2002 through 2012. Again, there is some skewing of the surveillance data, as 0.03 µg/mL was the lowest concentration of dalbavancin tested in that study. The MIC values are distributed in a unimodal manner in both the surveillance studies (≤ 0.03 µg/mL) and the clinical studies (≤ 0.03 µg/mL); the MICs ranged from ≤ 0.03 to 0.25 µg/mL in the SENTRY study and ≤ 0.001 to 0.015 µg/L in the clinical studies.

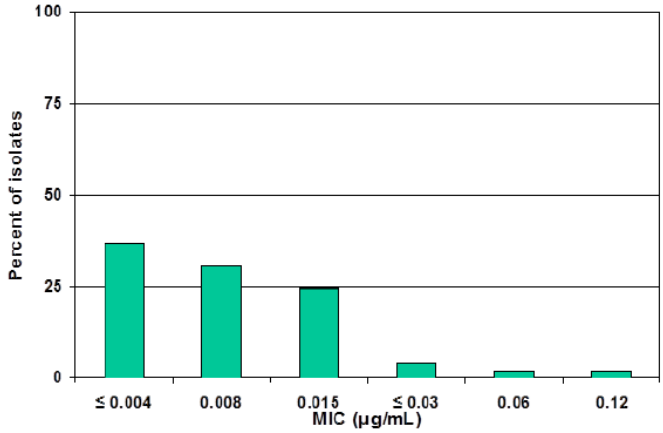
For *S. agalactiae* the MIC90 of dalbavancin in the surveillance studies was 0.06 µg/mL while the MIC90 in the clinical studies the MIC 90 was ≤ 0.03 µg/mL. There were only one isolate of 20 total isolates in the clinical trials and only 47 isolates of 2051 (2.3%) in the surveillance studies in the US with a MIC= 0.06 µg/ml. There were only one isolate of 20 total isolates in the clinical trials and only five isolates of 2051 (0.2%) in the surveillance studies in the US with a MIC= 0.12 µg/ml. There were no clinical isolates or surveillance isolates with a MIC ≥ 0.25 µg/ml.

Conclusion: Based on the surveillance and clinical trial data, a susceptibility breakpoint of 0.06 µg/mL for *S. agalactiae* would be appropriate. A susceptibility breakpoint of 0.25µg/mL for *S. agalactiae* would be inappropriate as there is so little clinical experience and so few surveillance isolates with this MIC.

***S. anginosus* group**

Data for baseline isolates of *S. anginosus* group streptococci from the abSSSI clinical trials are shown in Figure 13.

Figure 13. Dalbavancin MIC Distribution: *S. anginosus* Group Isolates from the abSSSI Clinical Trials



Source: Figure 24, Microbiology section, this submission.

Reviewer's comments: Surveillance data are available only for unspeciated viridans streptococci (1974 isolates). There were only nine clinical isolates in total. The Applicant is required to provide MIC data for a minimum of 100 isolates to qualify for the second list in the Microbiology section of the package insert. Consequently, the *S. anginosus* group does not qualify for inclusion in the second list. Also, due to the low number of clinical isolates, the *S. anginosus* group does not qualify for inclusion in the first list.

Conclusion: Based on the lack of surveillance and clinical trial data, the *S. anginosus* group cannot be included in either the first or second list in the Microbiology section of the package insert. Consequently, a susceptibility breakpoint cannot be assigned for the *S. anginosus* group.

ANIMAL STUDIES

The Applicant presented a summary of studies of animal infections with Staphylococci. These animal models include mice, rats and rabbit as well as immunocompetent and neutropenic models. Bacterial strains utilized in these studies were *S. epidermidis* and *S. aureus* (both methicillin susceptible and methicillin resistant). These studies were done in a variety of body sites in animals. The range of highest, efficacious MIC ran from 0.06 mcg/ml in neutropenic mice in the lung due to MSSA and subcutaneous implants in rabbits infected with MSSA to 4 mcg/ml in rabbits with endocarditis infected with MRSA and VISA.

(b) (4)

The Applicant presented a summary of studies of animal infections with Streptococci. These animal models include both mice and rats as well as immunocompetent and neutropenic models. Bacterial strains utilized in these studies were *S. pyogenes* and *S. pneumoniae* (both

penicillin susceptible and penicillin resistant). These studies were done in a variety of body sites in animals. The range of highest, efficacious MIC ran from 0.015 mcg/ml (in immunocompetent and neutropenic rats with lobar pneumonia due to PSSP and PSRP) to 0.25 mcg/ml (in immunocompetent rats with pneumonia infected with PRSP*).*

(b) (4)

Among the animal models listed above, the Applicant believes the neutropenic mouse thigh model was particularly relevant for the overall PK/PD analysis. Using dose fractionation studies with *S. aureus* and *S. pneumoniae* it was demonstrated that infrequent administration of larger mg/kg doses was more effective than administration of the same total dose as smaller, more frequent doses. Additionally, it demonstrated a relationship between AUC and MIC of the infecting organism and established target attainment ratios for AUC of free dalbavancin/MIC that were used in the Monte Carlo simulations discussed below. An additional consideration was the observation that plasma levels of free dalbavancin almost always exceeded the MIC throughout the course of these experiments, as is also the case in human plasma throughout the treatment period with the proposed dosages. The binding of dalbavancin to protein in human and mouse plasma was taken into account in the modeling.

PK/PD Analysis

Monte Carlo simulations were performed based on a number of factors. These included the MIC distributions and eradication rates for *S. aureus* and streptococci in the Phase 3 cSSSI and uSSSI clinical trials and the population PK of dalbavancin in patients. Because of the narrow range of MICs encountered in clinical studies and among surveillance isolates, wider MIC distributions were modeled based on PD considerations from the neutropenic mouse thigh model. These animal experiments demonstrated a relationship between efficacy and the ratio of free drug AUC to MIC for *S. aureus* and *S. pneumoniae*. However, an additional consideration was the observation that plasma levels of free dalbavancin almost always exceeded the MIC throughout the course of the experiments, as is also seen in human plasma throughout the treatment period with the proposed dosages. The binding of dalbavancin to protein in human and mouse plasma was taken into account in the modeling. Another consideration is that bactericidal concentrations of free dalbavancin are maintained over the entire treatment period in individuals receiving the proposed dosage.

These analyses support a susceptibility interpretive criterion for dalbavancin of ≤ 0.25 μg/mL.

CLINICAL STUDIES

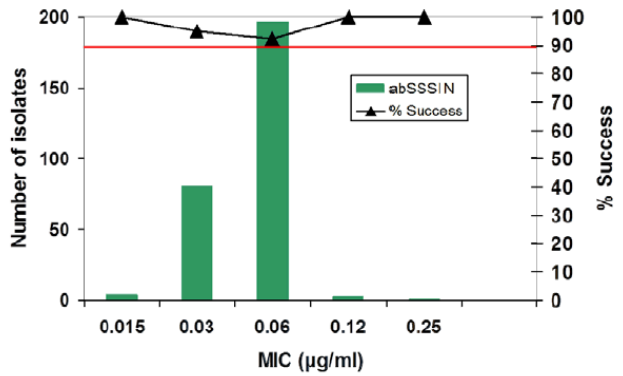
A discussion of the MIC characteristics of clinical isolates was presented in detail in the previous section on **DALBAVANCIN MIC FREQUENCY DISTRIBUTIONS.**

The by-pathogen microbiological success rate as a function of MIC is presented graphically below for key pathogens from the pooled abSSSI data base. It should be noted that microbiological success is generally equivalent to clinical success, because in skin infections an appropriate site for culture is rarely evident in cured patients.

Note that the clinical efficacy of dalbavancin was not related to MICs for baseline isolates from any species. This is illustrated by the clinical status of success at EOT and the investigator's assessment of clinical outcome at EOT as a function of baseline MIC in patients with a single baseline pathogen.

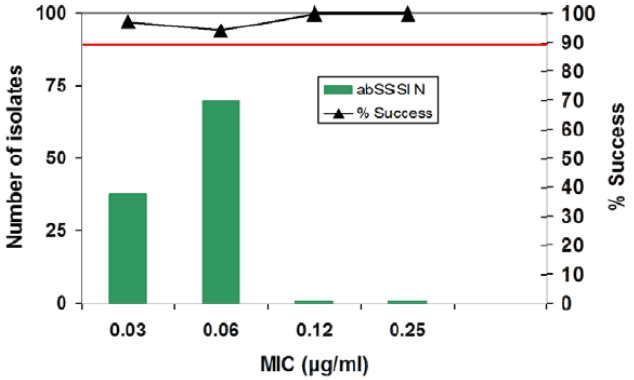
Dalbavancin Microbiological By-Pathogen Success vs. MIC: Pooled abSSSI Data, ME at EOT

Figure 14. *S. aureus*



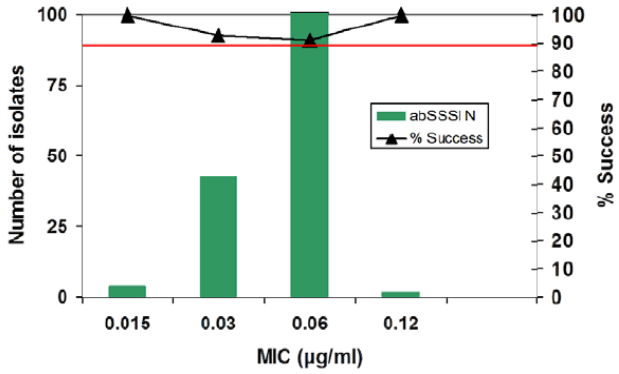
Source: Figure 29, Microbiology section, this submission.

Figure 15. MRSA



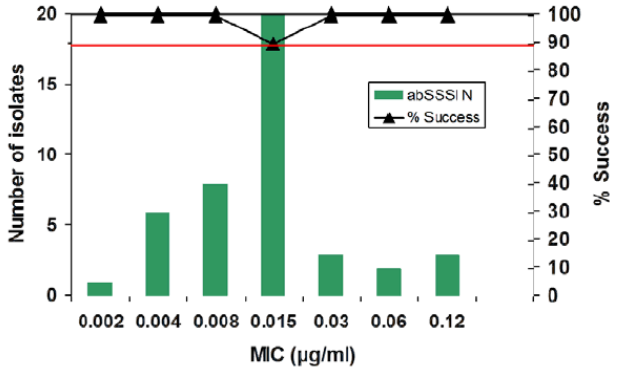
Source: Figure 30, Microbiology section, this submission.

Figure 16. MSSA



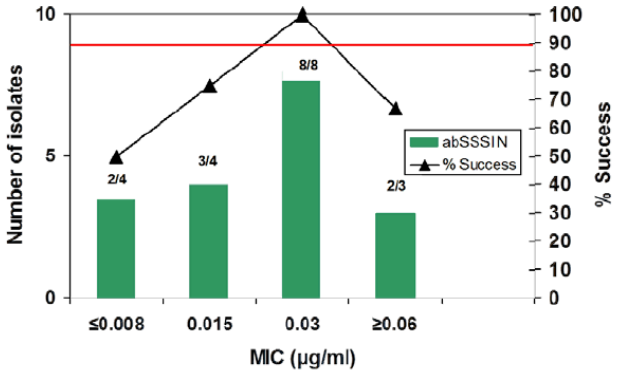
Source: Figure 31, Microbiology section, this submission.

Figure 17. *S. pyogenes*



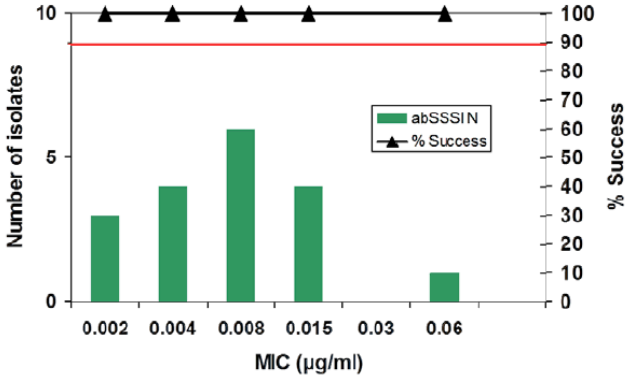
Source: Figure 32, Microbiology section, this submission.

Figure 18. *S. agalactiae*



Source: Figure 33, Microbiology section, this submission.

Figure 19. *S. anginosus* Group



Source: Figure 34, Microbiology section, this submission.

CONCLUSIONS

The Applicant proposes the susceptibility breakpoints for dalbavancin as ≤ 0.25 μg/mL for *S. aureus, S. pyogenes, S. agalactiae* and *S. anginosus* group. From the clinical microbiology perspective, the data provided by the Applicant do not provide sufficient clinical experience to support the Applicant's proposed breakpoint for susceptibility interpretive criteria of ≤ 0.25 μg/mL the target pathogens in the proposed Indication and Usage for dalbavancin.

In the table below, the breakpoint parameters derived from the various data for each pathogen are listed:

Table 23. Breakpoint Parameters for Each Pathogen (MIC= mcg/mL)

Breakpoint Parameter	*S. aureus*	*S. pyogenes*	*S. agalactiae*
Surveillance MIC90	0.06	0.03	0.06
Clinical isolate MIC90 or mode	0.06	0.015	0.03
PK/PD Monte Carlo simulations	0.25	0.25	0.25
Mouse thigh model MIC	0.12	0.03	0.03

If each parameter is weighted equally, the following MIC interpretive criteria were calculated for each pathogen:

Table 24. Weighted Average Breakpoints for Each Pathogen

Calclulation	Breakpoint (mcg/ml)	Pathogen
0.06(.25)+0.06(.25)+0.25(0.25)+0.12(.25)=	0.123	*S. aureus*
0.03(.25)+0.015(.25)+0.25(.25)+0.03(.25)=	0.081	*S. pyogenes*
0.06(.25)+0.03(.25)+0.25(.25)+0.03(.25)=	0.093	*S. agalactiae*

While none of these breakpoints are an exact MIC dilution, when approximated, each of these breakpoints is 0.12 μg/mL.

Thus, based on the data from the dalbavancin surveillance MICs, the clinical isolate MICs, the Monte Carlo simulations and the animal efficacy data, the Agency proposes the following interpretive criteria:

Table 25. MIC Susceptibility Test Result Interpretive Criteria for Dalbavancin

Pathogen	MIC (mcg/mL)			Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.12	--	--	--	--	--
Streptococcus pyogenes and *Streptococcus agalactiae*	≤ 0.12	--	--	--	--	--

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If an isolate yields an MIC result other than susceptible it should be retested being sure that the test is performed correctly. If the results are other than susceptible on re-test, the isolate should be submitted to a reference laboratory for testing.

There was no resistance to dalbavancin among any clinical trial isolates (either at baseline or emerging during therapy) or in worldwide surveys of clinical trial isolates, and no resistance has been generated in laboratory experiments. Thus, only a susceptibility breakpoint has been designated. In addition, no disk diffusion interpretive criteria are assigned due to the lack of a valid disk diffusion methodology.

Finally, the Agency agrees with the Applicant's proposed *in vitro* susceptibility test quality control parameters as indicated below:

Table 26. Acceptable MIC (µg/mL) Quality Control Ranges for Dalbavancin

QC Strain	MIC Range (mcg/mL)
Staphylococcus aureus ATCC ®29213	0.03-0.12
Streptococcus pneumoniae ATCC ® 49619a	0.008-0.03
Enterococcus faecalis ATCC ®29212	0.03-0.12

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

AGENCY RECOMMENDED MICROBIOLOGY PORTION OF THE PACKAGE INSERT

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. (b) (4)

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.

(b) (4)

Dalbavancin has been shown to be active against (b) (4) the following microorganisms, both *in vitro* and in clinical infections (b) (4)

Gram-positive bacteria
*Staphylococcus aureus (*including methicillin-resistant isolates)
Streptococcus pyogenes
Streptococcus agalactiae

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of (b) (4) exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptibility breakpoint for dalbavancin. However, the

safety and efficacy of dalbavancin in treating clinical infections due to these bacteria has not been established in adequate well-controlled clinical trials.

Gram-positive bacteria
*Enterococcus faecali*s (vancomycin-susceptible isolates only)
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 product 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 criteria provided in Table (b) (4)

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 (b) (4) 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)	≤ 0.12	--	--	--	--	--
Streptococcus pyogenes and *Streptococcus agalactiae*	≤ 0.12	--	--	--	--	--

[a] The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If isolates yield MIC results other than susceptible, they 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 using 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 7.

Table 7. Acceptable Quality Control Ranges for Dalbavancin

QC Strain	MIC Range (mcg/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

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

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(b) (4) 1547. The effect of broth medium on the *in vitro* activity of dalbavancin.

(b) (4) 1548: The effect of incubation temperature variation on the *in vitro* activity of dalbavancin.

VER001-MI-001. Effect of testing parameter variations on the *in vitro* activity of dalbavancin.

VER001-MI-003. Serial passages of isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis* in broth media containing dalbavancin to attempt to identify resistant mutants.

VER001-MI-004. Activity of dalbavancin against Gram-positive organisms.

VER001-MI-005. Dalbavancin compound interaction study.

VER001-MI-006. Dalbavancin, a new glycopeptide: Quality control studies for the microdilution MIC method.

VER001-MI-011. Time-kill kinetics of dalbavancin, teicoplanin, and vancomycin against *S. aureus*, *S. pyogenes*, and *E. faecalis*.

VER001-MI-012. Attempt to select spontaneous variants of *Staphylococcus aureus* and *Staphylococococus epidermidis* on agar media containing dalbavancin.

VER001-MI-013. Report of the pharmacodynamic activity of the glycopeptide, dalbavancin.

XRES-05062013. Evaluation of the potential of dalbavancin to select for reduced susceptibility in methicillin-resistant *Staphylococcus aureus*, including hVISA strains.

Peter Coderre, PhD
Clinical Microbiology Reviewer

Kerry Snow, MS
Clinical Microbiology Team Leader/DAIP
(for concurrence only)
25 February 2014

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/s/

PETER E CODERRE
02/25/2014

KERRY SNOW
02/26/2014

Product Quality Microbiology Review

12/20/2013

NDA 021883:

Drug Product Name
Proprietary: Dalvance
Non-proprietary: Dalbavanacin Hydrochloride

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
9/26/2013	9/26/2013	10/24/2013	10/24/2013
11/25/2013	11/25/2013	N/A	N/A
12/20/2013	12/20/2013	N/A	N/A

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
12/21/2004	1	5/13/2005
5/04/2005	1	5/13/2005

Applicant/Sponsor
Name: Durata Therapeutics, Inc.
Address: 200 South Wacker Dr
Suite 2550
Chicago IL 60606
Representative: Briton Shell, Director, Regulatory Affairs
Telephone: 203 871-4609

Name of Reviewer: Steven P. Donald, M.S.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: New Drug Application

2. SUBMISSION PROVIDES FOR: Manufacture and marketing of a sterile drug product

3. MANUFACTURING SITE:
(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lyophilized powder for injection; intravenous infusion; 500 mg in a glass vial

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

6. PHARMACOLOGICAL CATEGORY: Antibiotic for ABSSSI

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: Resubmission. Although a microbiology review of this NDA has been completed and no deficiencies were found, the proposed manufacturing facility has changed and a new microbiology review will be performed. Information requests were sent to the sponsor on 10/25/2013 and 12/04/2013; responses were received on 11/25/2013 and 12/20/2013.

filename: N021883r2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies –
No product quality microbiology deficiencies were identified based upon the information provided.

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

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

III. Administrative

A. Reviewer's Signature _____
Steven P. Donald, M.S.
Microbiology Reviewer

B. Endorsement Block_____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer

C. CC Block
N/A

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/s/

STEVEN P DONALD
12/24/2013

STEPHEN E LANGILLE
12/24/2013

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 21883 **Applicant:** Durata Therapeutics, Inc. **Letter Date:** 9/26/2013

Drug Name: Dalbavanacin Hydrochloride **NDA Type:** 505(b)(1) **Stamp Date:** 9/26/2013

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	x		CTD Format
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	x		See P.3.3.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	x		See P.3.5 for sterility assurance package
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?		x	PET testing is not required; C/C integrity testing not included but has been requested.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	x		See P.5.1 for sterility and endotoxin tests
7	Has the applicant submitted the results of analytical method verification studies?			See P.5.2 for sterility and endotoxin test validation
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	x		Post constitution hold time study has been submitted in P.2.6
10	Is this NDA fileable? If not, then describe why.	x		

Additional Comments: None

Steven Donald, M.S.	10/29/2013
Reviewing Microbiologist	Date
Stephen Langille, Ph.D.	10/29/2013
Microbiology Secondary Reviewer	Date

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/s/

STEVEN P DONALD
10/29/2013

STEPHEN E LANGILLE
10/29/2013

CLINICAL MICROBIOLOGY: 45-Day Meeting Checklist

NDA 21—883 SN000 Peter Coderre, PhD
Dalbavancin 22 October 2013
Durata Pharmaceutics

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?	√		
8	Has the applicant submitted the clinical microbiology datasets in a format which intents 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 intents 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 or nonstandardized methods for measuring microbiologic outcome? If nonstandardized 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 201.56 and 201.57 of the CFR, current Divisional policy.	√		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? **IF NO, GIVE REASONS BELOW.**	√		

Any Additional Clinical Microbiology Comments:

Peter Coderre, PhD
Reviewing Clinical Microbiologist

Kerry Snow, MS
Acting Team Leader
Clinical Microbiology
22 October 2013

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/s/

PETER E CODERRE
10/24/2013

KERRY SNOW
10/25/2013

Product Quality Microbiology Review

11 October 2007

NDA: 21-883 AZ

Drug Product Name
Proprietary: (b) (4)
Non-proprietary: Dalbavancin.
Drug Product Priority Classification: N/A.

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
19 JUN 2007	20 JUN 2007	05 JUL 2007	06 JUL 2007
17 SEP 2007	17 SEP 2007	N/A	N/A

Applicant/Sponsor
Name: Vicuron Pharmaceuticals Inc., a subsidiary of Pfizer.
Address: 235 East 42nd St. New York, NY. 10017
Representative: Helen Milton
Telephone: 860-732-1083

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommended for approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Amendment to original NDA.

2. SUBMISSION PROVIDES FOR: A complete response to the Approvable letter (21 JUN 2006). Included in the response are the following CMC issues:

- Endotoxin remediation update.
- The inclusion of the (b) (4) site for manufacture of Drug Substance.

3. MANUFACTURING SITE:

Following are the two drug substance manufacturing sites:

(b) (4)

Following is the drug product manufacturing site:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Lyophilized powder for injection in Type I glass vial.
- Intravenous injection.
- (b) (4) 500 mg in 50 mL vial.

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

6. PHARMACOLOGICAL CATEGORY: Antibiotic.

B. SUPPORTING/RELATED DOCUMENTS: Product Quality Microbiology Review of NDA 21-883 (review dated 13 May 2007) & Product Quality Microbiology Review of NDA 21-883GC (review dated 01 December 2006).

C. REMARKS:

The subject submission is a complete response to an approvable letter issued on 21 June 2006. Included in the response is an update regarding endotoxin remediation activities and information regarding the addition of a manufacturing site (b) (4)) for the manufacture of the drug substance. This review pertains to the endotoxin remediation information. The additional drug substance manufacturing site is not the subject of this review since the sterilization of the drug product takes place at a different manufacturing site following drug substance manufacture. Further, it is noted that the subject drug substance specifications include limits for both total microbes (NMT (b) (4) & NMT (b) (4)) and bacterial endotoxins (NMT (b) (4) [page 51 of 189 of the subject submission]. As a result, this review of the sterility assurance of the subject drug product is limited to review of the drug product sterilization process and manufacturing controls.

A memorandum was forwarded to the applicant on 27 August 2007 by the OND project manager on this reviewer's behalf for the purpose of requesting additional information. The following two questions and comments were forwarded to the applicant:

- The specification sheet lists the specification for bacterial endotoxins as (b) (4) (Table 3.2.P.5-1). This reviewer assumes that the "A" refers to "active", however the specification should be revised to "NMT (b) (4) to be consistent with industry reporting of values for bacterial endotoxins in drug products. The modified specification will also be consistent with the units provided for the drug substance endotoxin specification (Table 3.2.S.4-1).

- With regard to the bacterial endotoxins remediation strategy, the following statement describing the (b) (4)

The applicant provided a response to the above question/comment in a submission dated 17 September 2007. The applicant concurred with the suggestion to modify the drug product bacterial endotoxins specification units. In addition, the applicant provided detailed information regarding the (b) (4) (b) (4) of the drug substance. This information is provided in this review in the Section labeled Endotoxin Remediation.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 21-883AZ 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 – The subject drug substance is derived from the (b) (4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____
John W. Metcalfe, Ph.D.

B. Endorsement Block
James McVey

C. CC Block
In DFS

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/s/

John Metcalfe
10/22/2007 02:58:08 PM
MICROBIOLOGIST

James McVey
10/22/2007 03:07:31 PM
MICROBIOLOGIST

Product Quality Microbiology Review

01 December 2006

NDA: 21-883GC

Drug Product Name
Proprietary: (b) (4)
Non-proprietary: Dalbavancin.
Drug Product Priority Classification: N/A.

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
17 November 2006	29 November 2006	29 November 2006	30 November 2006

Applicant/Sponsor
Name: Pfizer, Inc.
Address: 235 East 42nd St.
New York, NY. 10017
Representative: Helen Milton
Telephone: 860-732-1083

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Comments to General Correspondence are provided.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: General Correspondence.

2. SUBMISSION PROVIDES FOR: A proposed bacterial endotoxin remediation plan with regard to manufacture of the drug substance.

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Lyophilized powder for injection in Type I glass vial.
- Intravenous injection.
- (b) (4) 500 mg in 50 mL vial.

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

6. PHARMACOLOGICAL CATEGORY: Antibiotic.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS: None.

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File Name: N021883GCR1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Not applicable.

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 – The subject submission proposes the addition of (b) (4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

C. Assessment of Risk Due to Microbiology Deficiencies – Not Applicable.

III. Administrative

A. Reviewer's Signature _____
John W. Metcalfe, Ph.D.

B. Endorsement Block
Bryan Riley, Ph.D.

C. CC Block
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/s/

John Metcalfe
12/4/2006 03:54:54 PM
MICROBIOLOGIST

Bryan Riley
12/5/2006 09:09:25 AM
MICROBIOLOGIST

DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS (HFD-520)

CLINICAL MICROBIOLOGY REVIEW #2

NDA 21-883 **DATE REVIEW COMPLETED: 17 May 06**
(Initial review completed 30 July 2005)

Dalbavancin
Pfizer (previously Vicuron)

INITIAL DOCUMENT DATE: 21 December 2004
INITIAL CDER DATE: 21 December 2004
INITIALED ASSIGNED DATE: 28 December 2004
INITIAL REVIEWER: Connie R. Mahon, MS, was initial primary reviewer prior to her leaving CDER for CVM

RESUBMISSION DATE: 20 December 2005
RESUBMISSION REVIEWER: Fred Marsik, Ph.D.
ADDITIONAL LABELING SUBMISSION: 5 MAY 2006

NAME AND ADDRESS OF APPLICANT:

Pfizer Global Pharmaceuticals
235 East 42nd street
New York, NY 10017

CONTACT PERSON:

Elina Srulevitch-Chin
Director/Team Leader
Worldwide Regulatory Strategy

DRUG PRODUCT NAME:
Non-Proprietary Name: Dalbavancin (V-Glycopeptide)
Proprietary Name: (b) (4)
Code name: VER001, BI 397, MDL 63, 397, or A-A-1
Chemical Name:

Dalbavancin A0 2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy42-(α-Dmannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59 hexaoxo2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosin-56yl]-2-[(9-methyldecanoyl)amino]-β-D-glucopyranuronic acid

Dalbavancin A1 2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42 (αDmannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59hexaoxo2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48 bis

NDA 21-883 **DATE REVIEW COMPLETED: 17 May 06**
(Initial review completed 30 July 2005)

Dalbavancin
Pfizer (previously Vicuron)

	(iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5*m*][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-[(undecanoyl)amino]-β D glucopyranuronic acid
Dalbavancin B0	2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-Dmannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaoxo 2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48 bis (iminomethano) -1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5*m*][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronic acid
Dalbavancin B1	2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-Dmannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaox2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5m*m*][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2 [(dodecanoyl)amino]-β-D-glucopyranuronic acid
Dalbavancin B2	2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-Dmannopyranosyloxy)-15-(dimethylamino)-2,16,36,50,51,59-hexaoxo 2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H* [1,14,6,22] dioxadiazacyclooctacosino[4,5*m*][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-[(10-methylundecanoyl)amino]-β-D glucopyranuronic acid

PROPOSED INDICATIONS AND USAGE: Treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* including methicillin-resistant and multi-drug resistant (MDR) isolates, *Streptococcus pyogenes*, and *Streptococcus agalactiae*

DOSAGE FORM: sterile, lyophilized, powder for intravenous administration (b) (4) 500 mg/vial.

DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS (HFD-520)

CLINICAL MICROBIOLOGY REVIEW #2

NDA 21-883 **DATE REVIEW COMPLETED: 17 May 06**
(Initial review completed 30 July 2005)

Dalbavancin
Pfizer (previously Vicuron)

ROUTE OF ADMINISTRATION STRENGTH, and DOSAGE/DURATION:
Intravenous, 1000 mg dose on Day 1 followed by a dose of 500 mg on Day 8

DISPENSED: Rx

RELATED DOCUMENTS: IND 60,613

PURPOSE OF SUBMISSION:

This New Drug Application (NDA) is submitted to seek approval for the use of intravenous dalbavancin for the treatment of complicated skin and skin structure infections in adults. This review provides comments regarding the clinical microbiology data submitted by the Applicant to support their proposal to manufacture and market dalbavancin. This review addresses the Applicant's proposed in vitro susceptibility testing interpretive criteria for broth microdilution testing against appropriate target pathogens. Disk diffusion method for dalbavancin (b) (4) and at present is not recommended for use for in vitro antimicrobial susceptibility testing.

REMARKS

The following review incorporates information from the original NDA submission (21 Dec 04) and information from the resubmission on 20 December 2005. The review also includes the microbiology portion or the modified dalbavancin package insert sent to the Agency by the Applicant on 5 May 06.

SUMMARY AND RECOMMENDATIONS:

1) From the clinical microbiology perspective, this NDA submission may be approved provided that the Applicant makes the changes in the microbiology subsection of the proposed label recommended by the Agency (See Agency's proposed microbiology section of the proposed label).

(b) (4)

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/s/

Frederic Marsik
5/17/2006 02:51:41 PM
MICROBIOLOGIST

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW

N 21-883 **DATE REVIEW COMPLETED: 30 July 2005**

DOCUMENT DATE: 21 December 2004
CDER DATE: 21 December 2004
ASSIGNED DATE: 28 December 2004
REVIEWER: Connie R. Mahon, MS

NAME AND ADDRESS OF APPLICANT:
Vicuron Pharmaceuticals
455 So Gulph Rd Suite 310
King of Prussia, PA 19406

CONTACT PERSON:
Judith Hoglind, PhD
Director
US Regulatory Affairs
Vicuron Pharmaceuticals
610-491-2200

DRUG PRODUCT NAME:
Non-Proprietary Name: Dalbavancin (V-Glycopeptide)
Proprietary Name: (b) (4)
Code name: VER001, BI 397, MDL 63, 397, or A-A-1
Chemical Name:

Dalbavancin A0 2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy42-(α-Dmannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59 hexaoxo2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosin-56yl]-2-[(9-methyldecanoyl)amino]-β-D-glucopyranuronic acid

Dalbavancin A1 2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42 (αDmannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59hexaoxo2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48 bis (iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5*m*][10,2,16]benzoxadiaza

	cyclotetracosin-56-yl]-2-[(undecanoyl)amino]-β D glucopyranuronic acid
Dalbavancin B0	2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-Dmannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaoxo 2,3,16,17,18,19,35,36,37,38,48,49,50,50 a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48 bis (iminomethano) -1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5 *m*][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronic acid
Dalbavancin B1	2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-Dmannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaox2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5m *m*][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2 [(dodecanoyl)amino]-β-D-glucopyranuronic acid
Dalbavancin B2	2-deoxy-l-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-Dmannopyranosyloxy)-15-(dimethylamino)-2,16,36,50,51,59-hexaoxo 2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H* [1,14,6,22] dioxadiazacyclooctacosino[4,5*m*][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-[(10-methylundecanoyl)amino]-β-D glucopyranuronic acid

PROPOSED INDICATIONS AND USAGE: Treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* including methicillin-resistant and multi-drug resistant (MDR) isolates, *Streptococcus pyogenes*, *Streptococcus agalactiae*, (b) (4)

DOSAGE FORM: sterile, lyophilized, powder for intravenous administration in (b) (4) 500 mg/vial.

ROUTE OF ADMINISTRATION STRENGTH, and DOSAGE/DURATION: Intravenous, 1000 mg dose on Day 1 followed by a dose of 500 mg on Day 8

DISPENSED: Rx

RELATED DOCUMENTS: IND 60,613

PURPOSE OF SUBMISSION:

This New Drug Application (NDA) is submitted to seek approval for the use of intravenous dalbavancin for the treatment of complicated skin and skin structure infections in adults. This review provides comments regarding the clinical microbiology data submitted by the Applicant to support their proposal to manufacture and market dalbavancin. This review addressed the Applicant's proposed in vitro susceptibility testing interpretive criteria for broth microdilution testing against appropriate target pathogens. Disk diffusion method for dalbavancin (b) (4) at present is not recommended for use for in vitro antimicrobial susceptibility testing.

SUMMARY AND RECOMMENDATIONS:

1) From the clinical microbiology perspective, this NDA submission may be approved provided that the Applicant makes the changes in the microbiology subsection of the proposed label recommended by the Agency (See Agency's proposed microbiology section of the proposed label).

(b) (4)

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/s/

Connie Mahon
9/19/2005 10:26:08 AM
MICROBIOLOGIST

Frederic Marsik
9/19/2005 10:40:00 AM
MICROBIOLOGIST

Lillian Gavrilovich
9/19/2005 11:43:07 AM
MEDICAL OFFICER

Product Quality Microbiology Review
Review for HFD-520

13 MAY 2005

NDA: 21-883

Drug Product Name
Proprietary: Trade Name To Be Established.
Non-proprietary: Dalbavancin for Injection.
Review Priority Classification: 1P.

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
21 DEC 2004	21 DEC 2004	19 JAN 2005	25 JAN 2005
04 MAY 2005	05 MAY 2005	N/A	N/A

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
N/A	N/A	N/A

Applicant/Sponsor
Name: Vicuron Pharmaceuticals Inc.
Address: 455 South Gulph Rd
Suite 310
King of Prussia, PA 19406
Representative: Dr. Judith Hoglind
Telephone: 610-491-2226

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommended for Approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA.

2. SUBMISSION PROVIDES FOR: A new drug product.

3. MANUFACTURING SITE:
Dalbavancin API will be manufactured by:
(b) (4)

Dalbavancin for Injection will be manufactured by:
(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Lyophilized powder for intravenous injection as a solution in a Type I glass vial.
- (b) (4) 500 mg in 50 mL vial.

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

6. PHARMACOLOGICAL CATEGORY: Antibiotic.

B. SUPPORTING/RELATED DOCUMENTS: Type V DMF (b) (4)

C. REMARKS:
The submission is electronic.

A phone call was placed by this reviewer to Dr. Judith Hoglind (applicant representative) on March 29, 2005 to ask the following questions. Applicant answers are provided in italics.

(b) (4)

2. Module 3.2.P.3 Table 4 provides a list of equipment used by the contract manufacturer and the relevant page numbers in DMF (b) (4) that provide sterilization validation information. (b) (4)

(Response Provided in email from Dr. Hoglind on April 1, 2005): (b) (4)

A phone call was placed on April 13, 2005 by this reviewer to Dr. Hoglind stating the following questions and comments. Applicant answers (emailed on 04 APR 2005) are provided in italics.

(b) (4)

(b) (4)

(b) (4)

File name: N021883R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 21-883 is recommended for approval from the standpoint of product quality microbiology.

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The subject drug product is (b) (4) at a subcontracting manufacturing laboratory.

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____
John W. Metcalfe, Ph.D.

B. Endorsement Block
David Hussong, Ph.D.

C. CC Block
In DFS

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/s/

John Metcalfe
5/17/05 09:28:02 AM
MICROBIOLOGIST

David Hussong
5/19/05 08:43:31 AM
MICROBIOLOGIST