CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(1) New Drug Application
Application Number	21883
Priority or Standard	Priority
Submit Date	09/26/2013
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Division / Office	Division of Anti-Infective Products / Office of Antimicrobial Products
Reviewer Name	Dmitri Iarikov, MD, PhD
Review Completion Date	02/27/14
Established Name	Dalbavancin hydrochloride (HCl)
Proposed Trade Name	DALVANCE
Therapeutic Class	Lipoglycopeptide antibacterial
Applicant	Durata Therapeutics International B.V.
Formulation	Sterile, lyophilized powder; Intravenous
Dosing Regimen	1000 mg on Day 1 and 500 mg on Day 8; for patients with creatinine clearance <30 mL/min and not on renal dialysis: 750 mg on Day 1 and 375 mg on Day 8.
Indication	Acute bacterial skin and skin structure infections (ABSSSI)
Intended Population	Adult

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

1.2 Risk Benefit Assessment

Dalbavancin demonstrated non-inferiority to the regimen of intravenous (IV) vancomycin with optional switch to oral linezolid for the treatment of ABSSSI in two phase 3 trials. The primary efficacy outcome was clinical response at 48 to 72 hours after study drug initiation defined as cessation of spread of ABSSSI and the absence of fever in the intent-to-treat (ITT) population. The prespecified noninferiority (NI) margin was 10%.

The trials also satisfied a key secondary endpoint in which clinical response was defined as a ≥20% reduction in lesion area from baseline (no fever component). Currently, this endpoint is recommended by the Agency as the primary endpoint for ABSSSI trials[1]. The lower bound of the 95% CI around the difference in clinical response rates was greater than -10 for this endpoint as well.

The success rates at later endpoints were lower in the dalbavancin arm than in the comparator arm in one of the phase 3 trials, DUR001-301. These secondary endpoints served to evaluate the maintenance of the clinical response achieved at 48-72 hours and included clinical success at end of treatment on Day 14 and at short term follow-up on Day 26-30. Of note, no noninferiority margin was prespecified for the later endpoints.

In trial DUR001-301 in the ITT population clinical success rates at EOT were 81.3% and 86.7% in the dalbavancin and comparator arms, respectively, a difference of -5.4%, 95% CI: (-11.5, 0.6). At the SFU visit the clinical response rate was 83.7% and 88.1% in the dalbavancin and comparator arms, respectively, a difference of -4.4%, 95% CI: (-10.2, 1.3). In trial DUR001-302, however, clinical response rates at later endpoints were somewhat higher in in the dalbavancin than in the comparator arms.

Dalbavancin demonstrated an overall favorable safety profile with similar rates of mortality and non-fatal adverse events as the comparators. The major safety finding is a

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

possibility of dalbavancin-associated liver injury, especially in subjects with underlying liver disease. This finding is based on an observation of several cases of high-degree transaminase enzyme elevations in dalbavancin-treated subjects which was not observed in the comparator group. None of these events was associated with fatal outcome or met Hy's law criteria. Liver tests abnormalities were documented to be resolved or significantly improved in all but two subjects who did not have follow-up measurements.

Another safety finding is a higher rate of adverse events related to hemorrhages in dalbavancin-treated subjects, including gastrointestinal and soft-tissue hemorrhages. All events of hemorrhages were non-fatal and whether this imbalance is due to chance or indeed associated with dalbavancin is uncertain.

In summary, the data submitted by the applicant demonstrate the acceptable safety profile of dalbavancin and provide evidence for approval of dalbavancin for the treatment of ABSSSI.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The reviewer considers routine pharmacovigillance a sufficient postmarket risk evaluation strategy for this NDA.

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric studies of dalbavancin in patients 0 to < 18 years of age will be requested. The design of these studies is to be determined. The required dalbavancin pediatric development program will likely include the following trials:

- A PK trial in children 0 to < 3 months of age
- A PK trial in children 3 months to < 12 years of age
- A safety and efficacy phase 3 clinical trial in patients with acute bacterial skin and structure infection (ABSSSI) aged 0 to 18 years of age

Of note, a single dose PK study in patients 12 to < 18 years has been already completed.

2 Introduction and Regulatory Background

2.1 Product Information

Dalbavancin is a lipoglycopeptide antibacterial drug proposed for the treatment of adult patients with ABSSSI caused by susceptible strains of the following Gram-positive microorganisms:

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

Figure 1 presents dalbavancin structure.

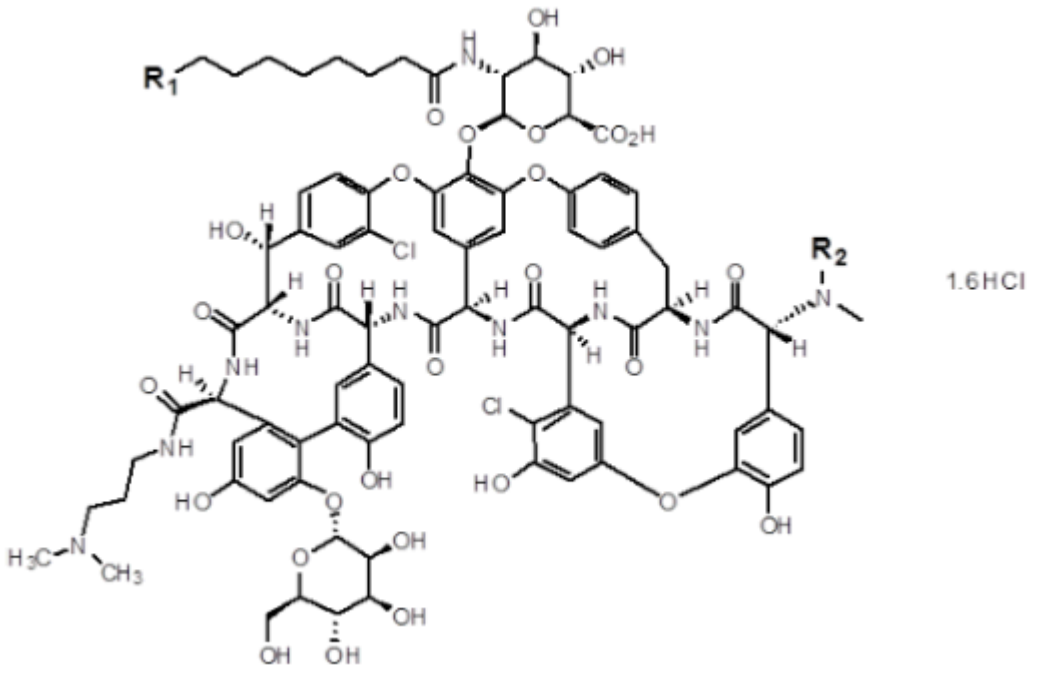

Figure 1: Dalbavancin structure

Because of its long elimination half-life the whole treatment regimen of dalbavancin is proposed to be administered as two intravenous injections, one on Day 1 and another on Day 8 at the following doses:

- Patients with CrCl ≥ 30 mL/min or patients receiving regular hemodialysis or peritoneal dialysis will receive 1000 mg dalbavancin on Day 1 and 500 mg on Day 8.
- Patients with CrCl < 30 mL/min who are not receiving regular hemodialysis or peritoneal dialysis will receive 750 mg dalbavancin on Day 1 and 375 mg on Day 8.

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

Dalbavancin is supplied in single-use vials containing dalbavancin hydrochloride equivalent to 500 mg dalbavancin as the free base. Inactive ingredients include mannitol, lactose and either sodium chloride or hydrochloric acid to adjust pH. Following reconstitution and further dilution, dalbavancin is administered via IV infusion over 30 minutes.

2.2 Tables of Currently Available Treatments for Proposed Indications

Products currently available for the treatment of skin and skin structure infections are presented in Table 1. The listing was created by searching the FDA Drug Label Database[2]. Antibacterial drugs with the following indications are included: skin and skin structure infections, skin and soft tissue infections, serious skin and soft tissue infections, complicated skin and skin structure infections, and acute bacterial skin and skin structure infection. Products labeled for the treatment of uncomplicated skin and skin-structure infections are not included.

Table 1: Products Labeled for the Treatment of Skin and Skin Structure Infections

Product Generic Name*	**Routes**
AMOXICILLIN AND CLAVULANATE POTASSIUM	Oral
AMIKACIN SULFATE	Intramuscular and Intravenous
AMPICILLIN, SULBACTAM	Intramuscular and Intravenous
AZTREONAM	Intravenous
CEFACLOR	Oral
CEFADROXIL HEMIDRATE	Oral
CEFAZOLIN SODIUM	Intravenous
CEFOTAXIME	Intramuscular and Intravenous
CEFOTETAN	Intravenous
CEFOXITIN	Intravenous
CEFTAROLINE FOSAMIL	Intravenous
CEFTAZIDIME	Intravenous
CEFTRIAXONE	Intramuscular and Intravenous
CEPHALEXIN	Oral
CIPROFLOXACIN	Intravenous and Oral
CLINDAMYCIN	Intravenous and Oral
DAPTOMYCIN	Intravenous
DEMECLOCYCLINE HYDROCHLORIDE	Oral
ERYTHROMYCIN	Oral
ERTAPENEM SODIUM	Intramuscular and Intravenous

2 http://ncsvmweb01.nctr.fda.gov/druglabel/

Table 1: Products Labeled for the Treatment of Skin and Skin Structure Infections	
Product Generic Name*	**Routes**
GENTAMICIN	Intramuscular and Intravenous
IMIPENEM AND CILASTATIN SODIUM	Intravenous
LEVOFLOXACIN	Intravenous and Oral
LINEZOLID	Intravenous and Oral
MEROPENEM	Intravenous
METRONIDAZOLE	Intravenous and Oral
MINOCYCLINE	Intravenous and Oral
MOXIFLOXACIN HYDROCHLORIDE	Intravenous and Oral
PIPERACILLIN SODIUM,TAZOBACTAM SODIUM	Intravenous
QUINUPRISTIN AND DALFOPRISTIN	Intravenous
TELAVANCIN HYDROCHLORIDE	Intravenous
TETRACYCLINE HYDROCHLORIDE	Oral
TIGECYCLINE	Intravenous
TOBRAMYCIN SULFATE	Intravenous
VANCOMYCIN HYDROCHLORIDE	Intravenous

2.3 Availability of Proposed Active Ingredient in the United States

Dalbavancin is a new molecular entity (NME) that is only available as an investigational agent.

2.4 Important Safety Issues with Consideration to Related Drugs

Dalbavancin is structurally related to vancomycin and may exhibit similar adverse reaction profile. The adverse reactions associated with vancomycin include infusion-related events including phlebitis and flushing of the upper body during rapid infusion, a.k.a. "red man syndrome", nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clinical trials of dalbavancin have been undertaken since 1999. Prior to acquisition of dalbavancin by Durata Therapeutics, Inc. (hereafter Durata) in December 2009, four other sponsors had developed dalbavancin under the names of VER001, PF-03906135, BI-397 and V-Glycopeptide. NDA 21-883 was initially submitted to FDA in December 2004 for the indication of complicated skin and skin structure infections (cSSSI) by Vicuron Pharmaceuticals Inc., a subsidiary of Pfizer.

The application was supported by a phase 3 trial in cSSSI (VER001-9). In this trial dalbavancin met the pre-specified criteria for non-inferiority to linezolid in the co-primary efficacy analyses of clinical response at test-of-cure (TOC) in the Intent-to-Treat (ITT) and in the Clinically Evaluable (CE) populations. The application also included a supportive study of uncomplicated skin and skin structure infections requiring parenteral therapy (VER001-8). Pfizer, however subsequently withdrew NDA 21-883 (b) (4)

Durata assumed the sponsorship of dalbavancin in December 2009 and in January 2011 initiated a clinical development program that included two new randomized phase 3 trials for the treatment of ABSSSI, DUR001-301 and DUR001-302. On September 26, 2013 Durata resubmitted NDA 21-883. The results of these two new trials are the main subject of this review. To date, dalbavancin has not been authorized for marketing in any country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submission are acceptable. The submission uses the electronic common technical document (eCTD) format. The submission is well organized and easy to navigate. Submitted Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets meet the Clinical Data Interchange Standards Consortium (CDISC) standards.

3.2 Compliance with Good Clinical Practices

The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that were consistent with Good Clinical Practice (GCP), International Conference on Harmonization (ICH) guidelines, and applicable regulatory requirements. Subjects provided written consent to participate in the study during the pre-randomization phase of the study after having been informed of the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

3.3 Financial Disclosures

See Appendix 9.4 Clinical Investigator Financial Disclosure for Financial Disclosure Review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dalbavancin is synthesized from a fermentation product of *Nonomuraea sp*. The drug substance, dalbavancin hydrochloride, is a semi-synthetic purified lipoglycopeptide. Dalbavancin hydrochloride is a mixture of 5 closely related homologs (A_0, A_1, B_0, B_1, and B_2). All homologues are microbiologically active and differ from one another in the length and/or branching of their fatty acid side chains on the N-acylaminoglucuronic acid moiety and/or the presence of an additional methyl group on the N-terminus of the peptide. The major homolog, B_0, composes >80% of the drug product.

The drug product is manufactured in [redacted] (b) (4) The chemistry reviewer concluded that the NDA has provided sufficient information to assure identity, strength, quality, purity, potency and bioavailability of dalbavancin and the finished drug product, dalbavancin for injection.

4.2 Clinical Microbiology

Dalbavancin is active against Gram-positive bacteria: methicillin-susceptible and methicillin-resistant *S. aureus* (MRSA), streptococci, and enterococci, including some strains of vancomycin-resistant enterococci (VRE). Dalbavancin is also active in vitro against anaerobic Gram-positive pathogens and against Gram-positive aerobic rods such as *Bacillus* spp., *Listeria* spp. and coryneforms.

With the exception of the vancomycin-resistant *S. aureus* (VRSA) strains, no staphylococci or streptococci resistant to dalbavancin have been identified among isolates from surveillance studies and dalbavancin clinical trials.

Resistance to dalbavancin among Gram-positive bacteria occurs in intrinsically glycopeptide-resistant species such as the genera *Pediococcus, and Lactobacillus* and to bacteria expressing the VanA phenotype of acquired resistance. VanA organisms, e.g. VanA enterococci are induced by glycopeptides to produce the D-alanyl-D-lactate terminus of the stem pentapeptides to which dalbavancin has low affinity. In contrast to vancomycin, however, dalbavancin is active against VanB and VanC enterococci. In these vancomycin-resistant organisms, dalbavancin does not induce the expression of altered dipeptide or it has sufficient affinity for another modified peptide terminus, D-alanyl-D-serine.

Dalbavancin minimal inhibitory concentration for at least 90% of strains tested (MIC_{90}) for aerobic Gram-positive cocci ranged from ≤0.03 to 0.12 µg/mL for most species. The

applicant proposes susceptibility breakpoints for dalbavancin of ≤ 0.25 µg/mL for all pathogens included in the proposed label, i.e. *S. aureus* including MRSA, *Streptococcus pyogenes*, *S. agalactiae*, and *S. anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*).

4.3 Nonclinical Pharmacology/Toxicology

The liver and kidney were the principal target organs in dalbavancin nonclinical studies. Liver and kidney toxicities occurred at 5-7 times the plasma exposure expected in humans. The adverse event that occurred at exposures comparable to clinical exposure was abortion in rabbits due to maternal toxicity. Overall, the major toxicities found by toxicology studies of dalbavancin were as follows:

- Liver toxicity in rats and dogs
- Renal toxicity in rats and dogs
- Abortions in rabbits
- Systemic and local infusion reactions

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

Liver Toxicity

- Observed at doses from 5-7 times the expected human dose on an exposure basis
- AST and ALT elevations were observed earlier than histologic changes and persisted after histologic findings had reversed. Thus, transaminase elevation in dogs persisted in the dog for more than 15 months after the end of the treatment period
- Histologic changes included dose-dependent hepatocellular necrosis

Renal Toxicity

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

Systemic Infusion Reactions

- Characterized by skin swelling and redness, salivation, vomiting, sedation, declines in blood pressure and increases in heart rate
- Observed only in dogs during or immediately following administration
- Observed predominantly at doses 15-20 times the human dose on a mg/kg/day basis
- Resolved within 1-hour post-dosing
- Attributed to histamine release

Injection Site Toxicity

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

Abortion attributed to maternal toxicity at exposures within the human therapeutic range was observed in rabbits with the no observed effect level of 0.7 times the human dose on an exposure basis. Of note, treatment of rabbits with antibacterial drugs often results in significant gastrointestinal effects that result in maternal toxicity. No evidence of teratogenicity associated with dalbavancin was demonstrated in rats or rabbits.

In an *in vitro* study, dalbavancin inhibited collagen-induced platelet aggregation. In this study that used rabbit platelets the 50% inhibitory concentration (IC50) of platelet aggregation was observed at dalbavancin concentrations of 494 mg/L and the maximal effect was obtained at ~1800 mg/L as compared with clinical C_{max} of 250 mg/L. This effect warrants special attention in light of a higher number of adverse events related to hemorrhage which were observed in the dalbavancin clinical trials (the reader is referred to section 7.3.4 Significant Adverse Events for further details).

Dalbavancin was widely distributed into tissues, but did not cross the blood brain barrier. Kidney, liver and aorta showed higher drug levels than plasma at both early time points through 70 days post-dose in the rat; thus 4.3% of the total dose was still present in the liver at day 70. Lymph nodes and the pancreas demonstrated vacuolization with no clear correlation to organ dysfunction. Dalbavancin was neither mutagenic nor clastogenic in the genetic toxicity studies. No carcinogenicity studies were deemed necessary because the drug is expected to be used short term.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Dalbavancin interrupts bacterial cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptides in emerging peptidoglycan and blocking the formation of cross-links that stabilize cell wall structure.

4.4.2 Pharmacodynamics

The unbound AUC_{0-24} to MIC ratio (AUC/MIC) was the PK-PD parameter best associated with in vivo efficacy of dalbavancin based on the neutropenic mouse thigh infection model. The activity of dalbavancin is time-dependent and *in vitro* studies suggested that time above the MIC is another important pharmacodynamic (PD) parameter.

Pharmacokinetic-pharmacodynamic (PK-PD) analyses for dalbavancin were conducted using individual predicted exposures and efficacy endpoints from one Phase 3 trial in patients with ABSSSI who received IV dalbavancin 1000 mg on Day 1 and 500 mg on Day 8. The univariate analyses demonstrated that:

- AUC_{avg}/MIC ratios ranging from 13,658 to 21,267 were associated with a higher percentage of patients achieving clinical or microbiological success at End of Therapy (EOT) or Test of Cure (TOC).
- AUC_{avg}:MIC ratios ranging from 13,396 to 16,096 were significantly associated with a higher percentage of patients achieving ≥ 10, 20, and 30% reduction from baseline in the area of infection on Day 4.

The PK-PD relationships between AUC_{avg}/MIC and clinical response at TOC or reduction in lesion size on Day 4 were used to develop in vitro interpretive criteria for dalbavancin against *S. aureus*. The mean percent probabilities of response by MIC are presented in **Table 2**.

Table 2: Mean model-predicted percent probabilities of response by MIC value for dalbavancin against *S. aureus*.

MIC	Mean model-predicted percent probability of response	
	Clinical success	≥ 20% reduction from baseline in the area of infection on Day 4
0.03	100	85.4
0.06	96.7	84.6
0.12	89.2	61.4
0.25	89.1	53.8

4.4.3 Pharmacokinetics

Dalbavancin mean C_{max} and AUC increased nearly proportional to dose, following single and multiple dose IV administration in healthy subjects. The mean clearance (CL) and steady state volume of distribution (Vss) remained relatively constant across all doses and after multiple-dose administration. In patients with infections, the mean CL and central volume of distribution (Vc) were 43% and 28% higher than those in healthy subjects, respectively. An initial dalbavancin dose of 1 gram IV followed 7 days later by a dose of 500 mg IV produces free concentrations above 1 mg/L throughout the entire 14-day treatment period. Dalbavancin plasma concentration-time profile is presented in Figure 2.

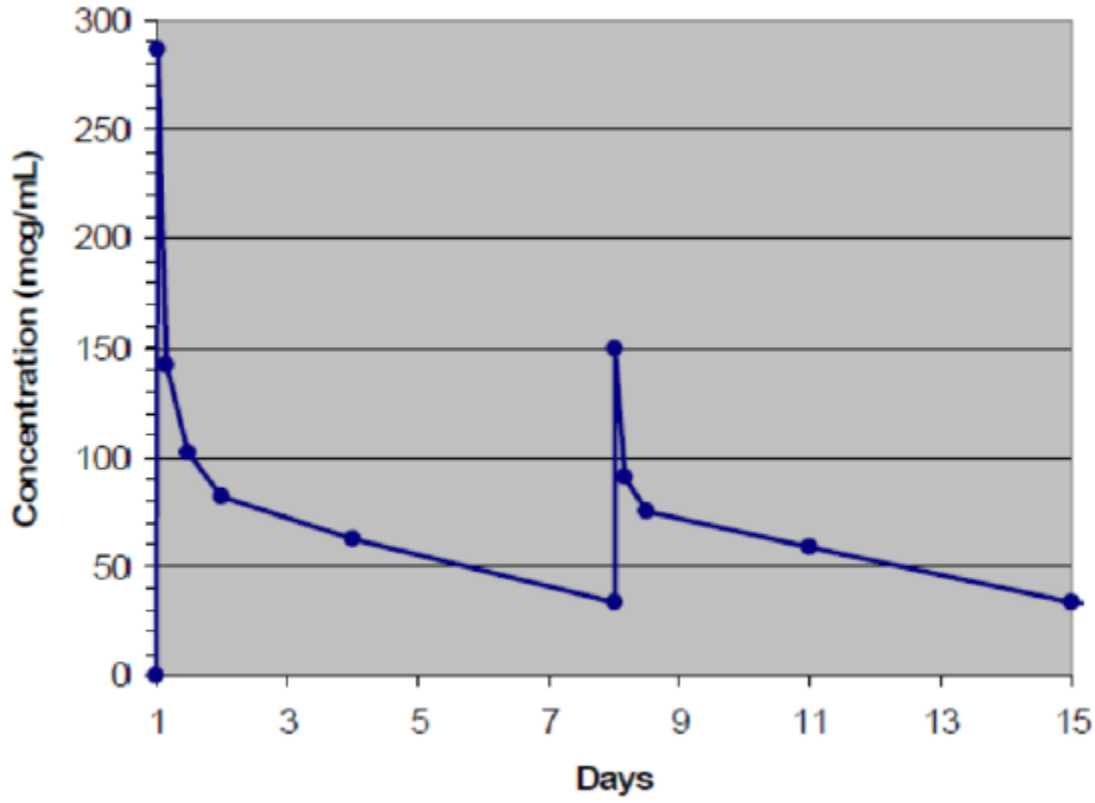

Figure 2: Mean dalbavancin plasma concentration in 10 healthy subjects receiving 1000 mg (Day 1) and 500 mg (Day 8)

Source: Figure 2, proposed dalbavancin label, submission module 1.14

Distribution
Following IV administration of 1000 mg dalbavancin, the mean steady-state apparent volume of distribution ranged from 11.2 L (0.14 L/kg) to 13.8 L (0.18 L/kg). Dalbavancin is reversibly bound to human plasma proteins, primarily albumin. The mean plasma protein binding of dalbavancin is approximately 93% and is independent of dalbavancin concentration. The tissue penetration of dalbavancin was with cantharides-induced skin blisters following administration of a single 1000 mg dose of dalbavancin. The mean percent penetration of dalbavancin in skin blister fluid was 60% as assessed in six healthy subjects.

Metabolism
In vitro studies using human microsomal enzymes demonstrated that dalbavancin was not a substrate or inhibitor of cytochrome P450 (CYP450) isoenzymes. A minor metabolite of dalbavancin (OH-dalbavancin) has been observed in the urine of healthy subjects and is below the assay lower limit of quantification (LLOQ) in plasma. OH-dalbavancin appears to have less antimicrobial activity than dalbavancin.

Excretion

Dalbavancin is excreted in both urine and feces. Following a single dose of 1000 mg dalbavancin, 27-45% of the administered dose was excreted in urine whereas 20% of the dose was excreted in feces. Of the dalbavancin excreted in the urine, 19-33% of the administered dose was excreted as unchanged dalbavancin and 8-12% of the dose as OH-dalbavancin.

Elderly/Gender/Race
The impact of covariates such as age, gender, and race on the PK of dalbavancin were evaluated with the population PK analysis. No appreciable changes in plasma clearance, central and peripheral compartments of distribution volume, or inter-compartment clearance were observed from patients aged 18 to 93 years, among male and female patients, and across races.

Pediatrics (adolescents)
The PK of dalbavancin were evaluated in hospitalized adolescents (12-16 years of age) receiving antibacterial therapy, following a dose of dalbavancin 1000 mg for those with body weight ≥60 kg or 15 mg/kg for <60 kg. Dalbavancin C_{max} and AUC_{inf} were comparable following these doses in adolescent patients. The mean C_{max} in adolescents receiving 1000 mg or 15 mg/kg dalbavancin was 26.1% or 33.4% lower than that in adults receiving single 1000 mg dose, respectively. The population PK analysis of data from patients indicated that the population mean of CL in adults appeared to be marginally lower than the mean in adolescents. The PK of dalbavancin in pediatric populations <12 years of age have not been evaluated.

Renal impairment
Dalbavancin does not seem to be eliminated by hemodialysis. In trial VER001-11, a 500-mg dose of dalbavancin was given to 6 subjects with end-stage renal disease; 3 subjects received dalbavancin pre-dialysis and 3 subjects received dalbavancin post-dialysis. No measurable concentrations of dalbavancin were found in the dialysate and there was no apparent reduction in dalbavancin concentration across arterial-venous sampling. Dalbavancin demonstrated similar concentration-time profiles regardless of whether dalbavancin was administered prior to or after the dialysis session.

Based on simulation results of individual concentration-time profiles from subjects with normal renal function and mild, moderate, and severe renal impairment, the proposed dosage regimen for patients with severe renal impairment not receiving hemodialysis is 750 mg on Day 1 and 375 mg on Day 8.

Hepatic impairment
The PK of dalbavancin was assessed in 17 subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) and 10 control subjects matched by

age, weight, and gender. The mean elimination half-life of dalbavancin remained unchanged. A dose adjustment is not proposed for subjects with hepatic impairment.

5 Sources of Clinical Data

The dalbavancin development program includes 21 clinical trials that enrolled 3442 subjects with 2085 subjects receiving at least one dose of dalbavancin. The trials include 14 phase 1 trials (n=431), two phase 2 trials (n=136), and five phase 3 trials (n= 2875), **Table 3**.

Table 3: Number of Subjects in Dalbavancin Development Program

	Phase 1	Phase 2	Phase 3 [a]	DUR001-301 and -302 [b]	All clinical trials
No of Trials	**14**	**2**	**5**	**2**	**21**
Dalbavancin	307	81	1704	659	2092
Comparator	124	55	1171	653	1350
Total	431	136	2875	1312	3442

[a] Including new phase 3 trials DUR001-301 and -302
[b] Included in the Phase 3 trials column

Fourteen phase 1 trials included 307 subjects who received dalbavancin and 124 subjects who received comparators, Table 4. These trials included three trials in special populations:

- Subjects with hepatic impairment, N=27 (hepatic impairment [n=17] and healthy subjects [n=10]), trial VER001-12
- Subjects with renal impairment, N= 48 (renal impairment [n=31], healthy subjects [n=15], and placebo [n=2]), trials VER001-3, VER001-11, and VER001-13. Of note, in trial VER001-3 only 3 subjects received dalbavancin at a single dose of 70 mg and the trial was terminated because the dose was deemed clinically irrelevant.

Two phase 2 clinical trials included VER001-4 for the treatment of catheter-related bloodstream Infections that enrolled 40 dalbavancin and 33 comparator treated subjects and VER001-5 for complicated skin and soft tissue infections (SSSI) that enrolled 41 dalbavancin and 21 comparator treated subjects.

Five phase 3 trials, Table 5, included 3 trials reviewed in the previous submission cycle (VER001-8, -9, -16) and 2 new trials (DUR001-301 and -302):

- VER001-8: uncomplicated skin and soft tissue infections; dalbavancin (N=367) vs. cefazolin (N=186)
- VER001-9: complicated skin and soft tissue infections, dalbavancin (n=571) vs. linezolid (N= 283)

- VER001-16: complicated or uncomplicated skin and skin structure infections in patients with suspected or confirmed MRSA, dalbavancin (N=107) versus vancomycin (N=49)
- DUR001-301: acute bacterial skin and skin structure infections, dalbavancin (N=288) versus vancomycin ± oral linezolid (N=285)
- DUR001-302: acute bacterial skin and skin structure infections, dalbavancin (N=371) versus vancomycin ± oral linezolid (N=368)

Overall, out of 1778 dalbavancin treated subjects in phase 2 and 3 clinical trials a total 1294 were treated for ABSSSI and cSSSI (trials VER001-5, VER001-9, VER001-16, DUR001-301 and DUR001-302), Table 5.

This review analyzes primarily two new phase 3 trials (DUR001-301 and DUR001-302). These non-inferiority trials were conducted under similar protocols and compared dalbavancin versus IV vancomycin with the option to switch to oral linezolid in the treatment of ABSSSI. Data from legacy trials were analyzed when deemed necessary.

5.1 Tables of Studies/Clinical Trials

Table 4: Phase 1 Pharmacokinetic Studies

Protocol / Study Period	Objective	Dalbavancin Regimen	Subjects
VER001-1 Aug 1999 – Nov 1999	Safety, maximum tolerated dose, PK of a single and multiple doses, and dose-limiting toxicities	Single dose: 70, 140, 220, 360 mg Multiple-doses (daily for 7 days) starting dose 70 mg Single or multiple dose IV placebo	23
VER001-2 Sep 2000-May 2001	Safety, dose limiting toxicities, maximum tolerated dose, PK, serum bactericidal activity and tissue penetration	Single dose: 140, 220, 350, 500, 630, 840, 1120 mg Multiple doses for 7 days: 300 mg on Day 1 given as 150 mg q12h followed by 30 mg/day for 6 Days Dose escalation as follows: 400/40 mg, 600/60 mg, 800/80 mg, 1000/100 mg. Single or multiple dose IV placebo	52
VER001-3 June 2001; terminated in Sep 2001 [a]	PK in subjects with mild to moderate renal impairment.	Single dose IV dalbavancin: 70 mg Single dose IV placebo	5
VER001-10 Dec 2001-Feb 2002	Concentrations of dalbavancin in skin tissues and the extent of its renal excretion	Single dose IV dalbavancin: 1000 mg	6
VER001-11 Sep 2003-June 2004	Safety and PK in subjects with severe renal impairment or end stage renal disease (ESRD)	Single dose of 500 or 1000 mg Group A: Severe renal impairment: A1: 500 mg; A2: 1000 mg Group B: ESRD B1: 500 mg prior to dialysis; B2: 500 mg after dialysis Group C: Healthy: 500 mg	22 A1= 6 A2= 4 B1= 3 B2=3 C= 6

Table 4: Phase 1 Pharmacokinetic Studies

Protocol / Study Period	Objective	Dalbavancin Regimen	Subjects
VER001-12 Jan 2003- Feb 2004	Safety, and PK in subjects with mild to severe hepatic impairment	1000 mg on Day 1 and 500 mg on Day 8 Group A: Mild hepatic impairment Group B: Moderate hepatic impairment Group C: Severe hepatic impairment Group D: Healthy	27 A= 6 B= 6 C= 5 D=10
VER001-13 Oct 2002- Aug 2003	Safety and PK in subjects with mild and moderate renal Impairment	Single dose 1000 mg Group A: Healthy Subjects Group B: Mild renal impairment Group C: Moderate renal impairment	21 A= 9 B= 6 C= 6
VER001-15 May 2004- Aug 2004	Effect of intravenous dalbavancin on the intestinal flora of healthy subjects	Single dose 1000 mg	12
VER001-19 Mar 2004- May 2004	Excretion of dalbavancin in healthy subjects	Single dose 1000 mg	9
A8841004 Sep 2008- July 2009	PK and safety in hospitalized adolescents aged 12–17 years receiving standard IV treatment for bacterial infections	1000 mg 15 mg/kg	10
DUR001-101 Mar 2011- Apr 2011	Plasma concentrations	Single dose 1500 mg	8
DUR001-102 Apr 2011- June 2011	Thorough QT study	Dalbavancin 1500 mg Dalbavancin 1000 mg moxifloxacin 400 mg PO Placebo IV	200
DUR001-103 June 2011- Feb 2012	PK and safety of a single 1000 mg dose of dalbavancin in healthy Japanese subjects	1000 mg 500 mg Placebo IV	18
DUR001-104 Mar 2012- July 2012	Safety and PK of dalbavancin administered weekly for 4 to 8 weeks to healthy adult subjects	1000 mg Week 1, 500 mg Weeks 2–4 1000 mg Week 1, 500 mg Weeks 2–6 1000 mg Week 1, 500 mg Weeks 2–8	18

[a] Study VER001-3 was prematurely terminated due to the Sponsor's decision to proceed with a higher, more clinically relevant dose.

Table 5: Phase 2 and Phase 3 Clinical Trials of Dalbavancin

Phase	Protocol / Study period	Indication / Design	Dose of Dalbavancin	ITT population [a]	
				Dalbavancin	Comparator
2	VER001-4 Apr 2002 – Sep 2003	Catheter-related bloodstream Infections / randomized, open-label	1) 650mg, then 65mg daily for 7- 14 days 2) 1000mg Day 1 ±500mg Day 8	N=40 1) n=7 2) n=33	Vancomycin N=34
2	VER001-5 July 2001 – June 2002	Complicated skin and soft tissue infections / randomized (1:1:1), open-label	1) 1100mg x 1 2) 1000mg Day1 ±500mg Day 8	N=41 1) n=20 2) n=21	N=21 Investigator Designated [b]
3	VER001-8 Dec 2002 – June 2004	Uncomplicated skin and soft tissue infections / randomized (2:1), double-blind	1000mg Day 1 ± 500mg Day 8	N= 367	Cefazolin / cephalexin N=186
3	VER001-9 Jan 2003 – May 2004	Complicated skin and soft tissue infections / randomized (2:1), double-blind	1000mg Day 1 +500mg Day 8	N =571	IV / Oral Linezolid N= 283
3	VER001-16 Oct 2003 - May 2004	Complicated or uncomplicated skin and skin structure infections in patients with suspected or confirmed MRSA / Randomized (2:1), open-label	1000mg Day 1 ± 500mg Day 8	N=107 cSSSI[c] n=30 uSSSI[d] n=77	Vancomycin N=49 cSSSI n=18 uSSSI n=31
	Total number of subjects in phase 2/3 trails included in the previous submission of NDA 21833			**1126**	**573**
3	DUR001-301 April 2011- Nov 2012	Acute bacterial skin and skin structure infections / randomized (1:1), double-blind	1000 mg on Day 1 and 500 mg on Day 8; for patients with creatinine clearance <30 mL/min and not on renal dialysis: 750 mg on Day 1 and 375 mg on Day 8.	N=288	Vancomycin ± oral linezolid N=285
3	DUR001-302 Sep 2011 - Dec 2012	Acute bacterial skin and skin structure infections / randomized (1:1), double-blind	1000 mg on Day 1 and 500 mg on Day 8; for patients with creatinine clearance <30 mL/min and not on renal dialysis: 750 mg on Day 1 and 375 mg on Day 8.	N=371	Vancomycin ± oral linezolid N=368
	Randomized subjects in two new phase 3 trials included in resubmission of NDA 21833			**659**	**653**
	Randomized subjects in dalbavancin and comparator arms in all phase 2 and 3 trials			**1785**	**1226**
	Received study drug in all phase 2 and 3 trials (Safety population)			**1778**	**1224**

[a] ITT – intent-to-treat population; for all but DUR001-301 and DUR001-302 trials the ITT includes subjects who received at least one dose of study drug whereas for DUR001-301 and DUR001-302 trials the ITT population included all randomized subjects regardless of study drug receipt; [b] Comparators for study VER001-5 included amoxicillin/clavulanate, aztreonam, cefazolin, ceftriaxone, cephalexin, clindamycin, gentamicin, levofloxacin, linezolid, piperacillin/tazobactam, and vancomycin in various combinations. [c] cSSSI – complicated skin and skin structure infections; [d] uSSSI – uncomplicated skin and soft tissue infections

5.2 Review Strategy

The review is focused on the results of two new clinical trials, i.e. DUR001-301 and DUR001-302. For the detailed review of clinical trials included in the previous submission cycle of NDA 21883 the reader is referred to the Safety Review by Dr. Menfo Imoisili and Efficacy Review by Dr. Janice Pohlman from September 2005.

5.3 Discussion of Individual Studies/Clinical Trials

Trials DUR001-301 and DUR001-302 were identical in design, non-inferiority, phase 3, double-blind, double-dummy, randomized trials comparing two weekly doses of dalbavancin (on Day 1 and Day 8) with vancomycin (with optional switch to oral linezolid) in patients with ABSSSI known or suspected to be caused by Gram-positive bacteria.

The primary efficacy outcome was clinical response, defined as cessation of spread of ABSSSI and the absence of fever at 48 to 72 hours after study drug initiation, in the intent-to-treat (ITT) population. Patients with missing data or who were lost to follow-up were classified as non-responders. The non-inferiority was concluded if the lower limit of the 95% confidence interval (CI) for the difference in percentage of responders at 48 to 72 hours (dalbavancin minus comparator) was > -10%.

Subjects were randomized in a 1:1 ratio to receive either two IV doses of dalbavancin (on Day 1 and Day 8) or up to 10 to 14 days of the comparator regimen. Enrollment of patients with major abscesses was capped at 30% of all patients. In addition, at least 40% of patients in trial DUR001-301 and 25% of patients in trial DUR001-301 were to have fever at Baseline.

The dose regimens in the dalbavancin arm were as follows:

- For subjects with creatinine clearance (CrCl) ≥30 mL/min and those receiving hemodialysis or peritoneal dialysis - 1000 mg on Day 1 and 500 mg on Day 8
- For subjects with a CrCl <30 mL/min and not on dialysis - 750 mg on Day 1 and 375 mg on Day 8. An IV placebo infusion was given q12h for between 3 and 14 days.

In the vancomycin/linezolid arm subjects received IV vancomycin q12h for between 3 and 14 days. Patients with normal renal function received vancomycin doses of 1000 mg or 15 mg/kg (depending on the study site standard of care). Subjects with impaired renal function had their dosage adjusted by an unblinded pharmacist. An IV placebo infusion was given on Days 1 and 8 to match the dalbavancin dosing regimen. Subjects could be switched to oral linezolid 600 mg q12h; subjects still received the placebo infusion on Day 8.

Following at least 72 hours of study drug treatment patients may have been switched from the twice daily IV study drug to oral therapy (oral linezolid 600 mg q12h for patients in the vancomycin/linezolid treatment group or matching placebo for patients in the dalbavancin treatment group), if both of the following conditions were met:

- In the previous 24 hours, the patient had 4 temperature measurements, each separated by approximately 6 hours, in which all 4 measurements were ≤37.6°C/99.7°F.
- There was unequivocal improvement in some or all of the clinical signs of the ABSSSI under study; if some signs had not improved, none should have worsened.

Baseline assessments were performed within 24 hours before the first dose; study treatment was initiated on Day 1. Efficacy and safety assessments were made on Days 2, 3, 4, 8, and 14 or 15 of the treatment period. An EOT assessment took place on Days 14 or 15, or within 3 days following premature discontinuation of treatment. The short-term follow-up visit (SFU) was to be targeted for Day 28, but could have occurred from Day 26 through Day 30. The long-term follow-up visit (LFU) was to be targeted for Day 70, but could have occurred from Day 60 through Day 88. Efficacy and safety assessments were also made at these visits.

The Schedule of Activities in the trials is presented in **Table 6**.

Table 6: Schedule of Selected Activities for Trials DUR001-301 and DUR001-302

	Study Visits								
	Baseline	Day 1	Day 2	Day 3	Day 4	Day 8	EOT (Day 14-15)	SFU (Day 26-30)	LFU (Day 60-88)
Informed consent	X								
Medical history and demographics	X								
Vital signs	X		X	X	X	X	X	X	X
Laboratory									
Hematology	X			X			X		
Chemistry	X			X			X		
Fasting glucose	X			X			X		
hs-CRP levels	X								
ASO/anti-DNase titers	X							X	
Pregnancy testing/FSH	X							X	
Electrocardiogram	X								
Blood culture [a]	X								
Systemic signs of infection [b]	X	X	X	X	X	X	X	X	X
Infection site assessment	X		X	X	X	X	X	X	X
Infection site specimen collection	X			X		X	X	X	X
Pain assessment	X			X			X		
Clinical status evaluation							X	X	
Investigator assessment of clinical response							X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

[a] Blood cultures were only to be drawn at Baseline (prior to study drug treatment) from 2 different anatomical sites and not through an existing intravascular line. If positive at Baseline, blood cultures were to be repeated every 48 to 72 hours until negative. If clinically indicated, blood cultures were to be collected at time of treatment discontinuation or for determination of treatment failure.
[b] On Days 1(after first dose of drug), 2, 4, 8, 28 and 70, the only systemic sign collected was temperature; hs-CRP was only collected at Baseline.
Abbreviations: ASO = antistreptolysin O; DNase = deoxyribonuclease; EOT = end-of-treatment visit; FSH = follicle-stimulating hormone; hs-CRP = high sensitivity C-reactive protein; LFU = long-term follow-up visit; SFU = short-term follow-up visit.

The following laboratory parameters were measured:

- Hematology: Complete blood count, including WBC and differential counts; at Baseline, Day 3 and Days 14 or 15
- Serum clinical chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, albumin, bilirubin, blood urea nitrogen or urea, creatinine, Na+, K+, Cl-, total CO_2 (bicarbonate), glucose, and lactate dehydrogenase at Baseline, Day 3 and Days 14 or 15.
- Serum hs-CRP levels: at Baseline only
- Banked serum sample: at Baseline and Day 3 only, to be used for retrospective safety assessments or exploratory analyses, as needed
- Serum for ASO/anti-DNase titers: at Baseline and SFU
- Pregnancy test (females of childbearing potential)/serum FSH (to confirm postmenopausal status for females <50 years of age or those ≥50 years of age who had been postmenopausal for <2 years): urine or serum (βhCG) only at Baseline; urine (βhCG) at SFU; FSH at Baseline only, as needed

If Gram-negative bacteremia was found to have been present at Baseline or developed during the study, the subject was removed from study treatment. Subjects with infections caused exclusively by Gram-negative bacteria (without Gram-positive bacteria present) and infections caused by fungi were excluded from the study. The patient was to have an EOT within 3 days following discontinuation of study treatment and AEs were to be reported through Day 70, at which time a status assessment was to be performed.

Subjects found to have had a Gram-positive organism at Baseline resistant to vancomycin, dalbavancin, and/or linezolid could have remained on study therapy based on the investigator's impression of the patient's clinical response to therapy.

Inclusion Criteria

1. Male or female patients 18 to 85 years of age
2. A personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) had been informed of all pertinent aspects of the study.
3. Patients having an ABSSSI (suspected or confirmed to be caused by Gram-positive bacteria) defined for purposes of this study as an infection either involving deeper soft tissue or requiring significant surgical intervention:

    a. Major cutaneous abscess characterized as a collection of pus within the dermis or deeper that was accompanied by erythema, edema and/or induration which:
        - required surgical incision and drainage, and
        - was associated with cellulitis such that the total affected area involved at least 75 cm^2 of erythema, and

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

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

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

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

5. Patients must have presented with at least one of the following systemic signs 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

6. Infection severity such that a minimum of 3 days of IV therapy was appropriate for management of the ABSSSI.
7. Patient was willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria

1. Patients with a contraindication to the administration of dalbavancin, vancomycin, or linezolid, such as hypersensitivity to any of the agents.
2. Females of childbearing potential who were unable to take adequate contraceptive precautions, had a positive pregnancy result within 24 hours prior to study entry, were known to be pregnant, or were currently breastfeeding an infant.
3. Patients with sustained shock, defined as systolic blood pressure <90 mm Hg for more than 2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion or need for sympathomimetic agents to maintain blood pressure.
4. Participation in another study of an investigational drug or device within 30 days before this study began.
5. Receipt of a systemically or topically administered antibiotic with a Gram-positive spectrum that achieved therapeutic concentrations in the serum or at the site of the ABSSSI within 14 days prior to randomization. An exception was allowed for patients receiving a single dose of a short-acting (half-life ≤12 hours) antibacterial drug ≥3 days prior to randomization (e.g., administration of a single dose of an antibacterial drug for surgical prophylaxis).
6. Infection due to an organism known prior to study entry to be resistant to dalbavancin or vancomycin (vancomycin mean inhibitory concentration >8 µg/mL).
7. Patients with evidence of meningitis, necrotizing fasciitis, gas gangrene, gangrene, septic arthritis, osteomyelitis; endovascular infection, such as clinical and/or echocardiographic evidence of endocarditis or septic thrombophlebitis.
8. Infections caused exclusively by Gram-negative bacteria (without Gram-positive bacteria present) and infections caused by fungi, whether alone or in combination with a bacterial pathogen.
9. Venous catheter entry site infection.
10. Infections that involved diabetic foot ulceration, a perirectal abscess or a decubitus ulcer.
11. Patient with an infected device, even if the device was removed. Examples included infection of: prosthetic cardiac valve, vascular graft, a pacemaker battery pack, joint prosthesis, hemodialysis catheter, implantable pacemaker or defibrillator, intra-aortic balloon pump, left ventricular assist device, a peritoneal dialysis catheter, or a neurosurgical device such as a ventricular peritoneal shunt, intracranial pressure monitor, or epidural catheter.
12. Gram-negative bacteremia, even in the presence of Gram-positive infection or Gram-positive bacteremia. Note: If a Gram-negative bacteremia developed during the study, or was subsequently found to have been present at Baseline, the patient was removed from study treatment and received appropriate antibiotic(s) to treat the Gram-negative bacteremia. Such patients were to have an EOT performed within 72 hours after discontinuing study medication, but were required to have AEs reported through Day 70, and a patient status at Day 70.
13. Patients whose ABSSSI was the result of having sustained full or partial thickness burns.

14. Patients with an infection involving a limb with evidence of critical ischemia defined as any of the following criteria: absent or abnormal Doppler wave forms, toe blood pressure of <45 mm Hg, ankle brachial index <0.5, and/or critical ischemia as assessed by a vascular surgeon.
15. Patients with ABSSSI such as superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that only required surgical drainage for cure.
16. Concomitant condition requiring any antibiotic therapy that would have interfered with the assessment of study drug for the condition under study.
17. Anticipated need of antibiotic therapy for longer than 14 days.
18. Patients who were placed in a hyperbaric chamber as adjunctive therapy for the ABSSSI.
19. More than 2 surgical interventions (defined as procedures conducted under sterile technique and typically unable to be performed at the bedside) for the ABSSSI, or patients who were expected to require more than 2 such interventions.
20. Medical conditions in which chronic inflammation may have precluded assessment of clinical response to therapy even after successful treatment (e.g., chronic stasis dermatitis of the lower extremity).
21. Absolute neutrophil count <500 cells/mm^3.
22. Known or suspected human immunodeficiency virus (HIV) infected patients with a cluster of differentiation (CD) 4 cell count <200 cells/mm^3 or with a past or current acquired immunodeficiency syndrome (AIDS)-defining condition and unknown CD4 count.
23. Patients with a recent bone marrow transplant (in post-transplant hospital stay).
24. Patients who were receiving oral steroids >20 mg prednisolone per day (or equivalent) or receiving immunosuppressant drugs after organ transplantation.
25. Patients who were receiving an antipyretic drug on a daily basis (e.g., daily use of naproxen) whose regimen could not be modified during the first 3 days of study drug therapy.
26. Patients with a rapidly fatal illness, who were not expected to survive for 3 months.
27. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into the study.
28. Prior participation in study DUR001-301 or DUR001-302.

Analysis Populations

Six main subject populations were identified for primary and secondary efficacy analyses:

- Intent-to-treat (ITT) – all randomized patients
- Clinically evaluable (CE) populations – three CE populations are defined based on the timing of outcome assessment: clinically evaluable at the end-of-treatment visit (CE-EOT), clinically evaluable at the long-term follow-up visit (CE-LFU), clinically evaluable at the short-term follow-up visit (CE- SFU)

Subjects who met all of the following criteria were considered to be clinically evaluable:

- Fulfilled inclusion/exclusion criteria such that the clinical response was not confounded
- For subjects randomized to dalbavancin, received at least 1 dose of active study drug; for subjects randomized to vancomycin/linezolid, received at least 50% of the expected doses of study drug; or received a minimum of 3 days of study drug (including placebo) for failures and 5 days of study drug (including placebo) for clinical successes
- Received no more than 1 dose of another systemic antibacterial therapy (with the exception of systemic aztreonam, oral or intravenous (IV) metronidazole, or oral vancomycin) with documented activity against the causative organism from study drug initiation until the outcome assessment (visit) for a non-ABSSSI indication [Note: subjects who received a new non-study systemic antibacterial treatment (with the exception of aztreonam or metronidazole) for treatment of the ABSSSI from initiation of study drug through the outcome assessment visit were assessed as evaluable failures.]
- Had an outcome assessment at which a clinical response could be evaluated
- Received appropriate adjunctive antibacterial coverage if the subject had a culture documented mixed ABSSSI (1 or more Gram-positive pathogens with 1 or more Gram-negative aerobic or anaerobic organisms).
- In addition, subjects must have met the following to be included in the CE populations:
    - For the CE-EOT population: completed the EOT assessments such that the patient could be defined as a clinical success or failure and the EOT assessments occurred on Day 14 to 15 (unless the patient was considered a clinical failure prior to Day 14 to 15). If the last dose of study drug was on Day 15, the EOT assessment could have occurred on Day 16.
    - For the CE-SFU population: completed the SFU assessments such that the patient could be defined as a clinical success or failure, unless the patient was considered a clinical failure at EOT and the SFU assessments occurred on Days 26 to 30, unless the patient was considered a clinical failure at EOT.
    - For the CE-LFU population: Completed the investigator's assessment of response (i.e., was deemed either a continued success or a relapse/recurrence) at LFU; and the LFU occurred on Days 60 to 88.

- Microbiological intent-to-treat (micro-ITT) – all subjects in the ITT population with at least 1 Gram-positive bacterial pathogen isolated at baseline. The Gram-positive bacterial pathogen must be identified from a blood culture or from a culture of a microbiological sample obtained from the primary ABSSSI site from an acceptable source.

- Microbiologically evaluable (ME) - all patients who were in both the CE-EOT and the microITT populations

In addition, for the purpose of safety evaluation, the Safety population was defined as all subjects in the ITT population who received at least one dose of study drug.

The secondary outcome was clinical status at EOT (Day 14-15) in the CE-EOT and ITT populations. Clinical status was also determined at short term follow-up (SFU) in the CE-SFU and ITT populations. Secondary efficacy outcome measures included evaluation of clinical status at the EOT and SFU visits.

Clinical success was defined based on the following:

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

Clinical failure was declared if at least 1 of the following criteria was met:

- The patient's lesion size as defined by erythema, was not decreased from Baseline
- Local signs of fluctuance and localized heat/warmth had not resolved
- Local signs of tenderness to palpation and swelling/induration were worse than mild
- For patients with a wound infection, the severity of the purulent drainage was the same or worsened relative to Baseline or was worse than mild
- The patient had a temperature of >37.6° C (by any measurement method) at the visit
- The patient received a new non-study systemic antibacterial treatment for the ABSSSI at any time from the first dose of study drug through the visit
- The patient died during the study period up to the visit
- Unless preplanned as part of non-drug therapy for the ABSSSI, the patient required surgical intervention more than 72 hours after the start of therapy for treatment of the ABSSSI under study
- The patient received study therapy for the ABSSSI under study beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy was needed for treatment of the underlying skin infection

Patients were defined to have an indeterminate outcome if any data needed to determine whether the outcome was success or failure, were missing. Patients with an

indeterminate response were included in the denominator for analyses in the ITT and microITT populations, and were counted as failures.

Additional efficacy outcome measures were:

- Resolution of local signs of infection
- Resolution of fever, for those with fever at Baseline
- Subjects' assessments of pain
- Investigator's assessments of Clinical response at EOT and SFU
- Investigator's assessment of clinical response at LFU
- Per-pathogen and per-subject microbiologic response to therapy

Investigator assessment was less specific and required resolution of improvement in signs and symptoms to declare clinical success. Criteria for success for clinical status definition and investigator assessment are summarized in **Table 7**.

Table 7: Criteria for Clinical Success as per Clinical Status Definition and Investigator Assessment

Criteria for Success	Clinical Status Definitions	Investigator Assessment Definitions
Lesion area (as defined by erythema)	Decreased from Baseline	Resolution or improvement
Temperature	≤37.6° C	Resolution or Improvement
Local signs of fluctuance/ localized heat/ warmth	Absent	Resolution or Improvement
Local signs of tenderness to palpation and swelling/ induration	No worse than mild	Resolution or Improvement
Purulent drainage (only for patients with wound infection)	Severity improved and no worse than mild relative to Baseline	Resolution or improvement
Concurrent antibiotic for primary infection	None	None
Surgical intervention for ABSSSI	None unplanned >72 hours	None unplanned >72 hours
Survival	Alive	Alive

Additional efficacy analyses included:

- Concordance analysis of clinical response at 48-72 hours and clinical status at EOT in the ITT population.
- Clinical status at the EOT visit in the microITT and ME population.
- Clinical status at the SFU visit in the ITT and CE-SFU populations.

- Investigator's assessment of clinical response at the EOT and SFU visits in the ITT and CE-EOT and CE-SFU populations.
- Investigator's assessment of status at the LFU visit in the CE-LFU population.
- Clinical success defined as resolution of all local signs and no fever at the EOT visit (ITT and CE-EOT populations) and SFU visit (ITT and CE-SFU populations).
- The proportion of clinical responders by key target pathogen [*S. aureus* (including MSSA and MRSA), *S. agalactiae, S. pyogenes,* Group C β-hemolytic streptococci*, S. anginosus-milleri* Group*, E. faecalis, E. faecium*] at Early Clinical response for the microITT population.
- The proportion of patients with a clinical status of success by key target pathogen at the EOT visit for the microITT and ME population
- Clinical success defined as resolution of all signs and symptoms at the EOT visit (ITT and CE-EOT populations) and SFU visit (ITT and CE-SFU populations)

The submission also includes a legacy trial, VER001-9, titled "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 soft tissue infections with suspected or confirmed Gram-positive bacterial pathogens." The trial was submitted and reviewed during the initial submission of the NDA. Due to significant differences between two new trials DUR001-301 and -302 and trial WER001-9, this trial was not used in the efficacy analysis, **Table 8**.

Table 8: Key differences in the design of VER001-09 and DUR001-301 and -302 trials

	VER001-09	DUR001-301 and -302
Comparator	Linezolid IV and orally	Vancomycin IV and linezolid orally
Dalbavancin: comparator randomization ratio	2:1	1:1
Timing of clinical response determination for the primary efficacy outcome	On 14 ± 2 days after completion of therapy	At 42-72 hours after initiation of treatment
Primary efficacy endpoint population	Clinically evaluable	Intent-to-treat
Area of cellulitis of >75cm^2 for all subtypes of infection	Not required as an inclusion criterion	Required as an inclusion criterion
Subjects with urine output of <20 cc/hour averaged over 24 hours	Excluded	Allowed
Subjects with creatinine clearance ≤ 50 ml/min	Excluded	Allowed
Subjects with bilirubin > 2x the upper limit of normal	Excluded	Allowed

Table 8: Key differences in the design of VER001-09 and DUR001-301 and -302 trials

	VER001-09	DUR001-301 and -302
Minimum number of days of parenteral therapy warranted	1	3

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Dalbavancin is being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI).

6.1.1 Methods

Efficacy analyses are based on the results of DUR001-301 and DUR001-302 trials. The design of the trials is presented in section 5.3 Discussion of Individual Studies/Clinical Trials.

The primary efficacy outcome measure was clinical response (cessation of spread of lesion, and the absence of fever) at 48 to 72 hours. Patients who met these criteria were classified as responders. Patients who used any non-study systemic antibacterial drugs or died within 48-72 hours were counted as non-responders. The primary efficacy analysis was performed in the ITT population.

A 2-sided 95% CI for the observed difference in primary outcome rates (dalbavancin treatment group minus vancomycin/linezolid treatment group) was calculated. The non-inferiority of dalbavancin to vancomycin/linezolid was concluded if the lower limit of the 95% CI for the treatment difference in the ITT population exceeded –10%.

Patients with missing data were defined as a non-responder for the primary analysis. The patient was considered to have missing data if there was no lesion measurement at baseline and/or in the 48 to 72 hour time period. In addition, the patient was considered to have missing data if there were not 3 temperature measurements in the 48 to 72 hour time period taken 6 hours apart.

The FDA also considered clinical response rates at 48-72 hours in which clinical response was defined as a ≥20% reduction in lesion area from baseline (no fever

component) as a key secondary endpoint. This endpoint is recommended as the primary efficacy endpoint by the current guidance for ABSSSI[3].
The success rates at later endpoints that served to evaluate the maintenance of the clinical response achieved at 48-72 hours were also conducted. These endpoints included clinical success at end of treatment (EOT) and short term follow-up (SFU), Day 26-30. Of note, no noninferiority margin was prespecified for the later endpoints.

6.1.2 Demographics

Demographics and baseline characteristics in trials DUR001-301 and -302 are presented in **Table 9**.

Table 9: Demographic and Baseline Characteristics (ITT Population)

	DUR001-301 and -302	
	Dalbavancin (N=659) n (%)	**Comparator (N=653) n (%)**
Age (years)		
Mean (SD)	49 (16)	50.3
Median	49	51
Min, Max	18,85	18,84
< 65	552	529
≥ 65	107	124
Gender N (%)		
Male	393 (59.6)	374 (57.3)
Female	266 (40.4)	279 (42.7)
Race N (%)		
White	592 (89.8)	579 (88.7)
Black or African American	29 (4.4)	36 (5.5)
Asian	28 (4.2)	32 (4.9)
American Indian or Alaska Native	5 (0.8)	4 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.2)
Other	4 (0.6)	1 (0.2)
Creatinine Clearance		
< 30 mL/min	19 (2.9)	14 (2.1)
30-59 mL/min	121 (18.4)	124 (19)
60-89 mL/min	195 (29.6)	191 (29.2)
≥ 90 mL/min	304 (46.1)	311 (47.6)
Unknown	20 (3)	13 (2)
Baseline Hepatobiliary Status		
Elevated [a]	33 (5)	39 (6)

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

Table 9: Demographic and Baseline Characteristics (ITT Population)		
	DUR001-301 and -302	
	Dalbavancin (N=659) n (%)	**Comparator (N=653) n (%)**
Not Elevated	574 (87.1)	577 (88.4)
Unknown	52 (7.9)	37 (5.7)
BMI (kg/m^2); Safety Population		
Mean (SD)	29.2 (7.2)	29.1 (7.2)
Median	27.5	27.6
Min, Max	14,69	17,65
BMI (kg/m^2) Distribution N (%)		
Underweight (<18.5)	5 (0.8)	9 (1.4)
Normal Weight (≥18.5, <25)	180 (27.3)	203 (31.1)
Overweight (≥25)	473 (71.8)	440 (67.4)
Unknown	1 (0.2)	1 (0.2)
Location n (%)		
North America	238 (36.1)	235 (36)
Eastern Europe/South Africa	396 (60.1)	390 (59.7)
Asia / Pacific	25 (3.8)	28 (4.3)

[a] Baseline hepatobiliary status: elevated if either baseline ALT or AST was >3 times the ULN, or if the subject's baseline alkaline phosphatase level was >1.5 times the ULN
ITT – intention to treat
Source: Generated from ISS Phase 2/3 ADSL analysis dataset, module 5.3.5.3

Of the 652 subjects who received dalbavancin in these trials, 395 (60.6%) were enrolled in an Eastern European or South African study center, 233 (35.7%) were enrolled in a North American study center, and 24 (3.7%) were enrolled in an Asian-Pacific study center.

The distribution of the subjects by infection type in the ITT population in DUR001-301 and -302 trials as well as infection area baseline measurements are presented in the table on the following page. Cellulitis was the most common type of infection, diagnosed in more than 50% of dalbavancin- and comparator-treated subjects in both trials. There were somewhat more subjects with abscesses in the comparator than in the dalbavancin arm in trial DUR001-301, 86 (30.2%) versus 72 (25%), respectively.

Table 10: ABSSSI Infection Types in the ITT population in DUR001-301 and DUR001-302 Trials

	DUR001-301		DUR001-302	
	Dalbavancin N=288 n (%)	Comparator N=285 n (%)	Dalbavancin N=371 n (%)	Comparator N=368 n (%)
Cellulitis	156 (54.2)	147 (51.6)	198 (53.4)	202 (54.9)
Major Abscess	72 (25)	86 (30.2)	90 (24.3)	87 (23.6)
Wound Infection	60 (20.8)	52 (18.2)	82 (22.1)	79 (21.5)
Not described	0	0	1 (0.3)	0

In both trials infections were most commonly located on the lower extremities. Thus in trial DUR001-301 a total of 145 (50.3%) infections in the dalbavancin group and 144 (50.5%) infections in the comparator group were located on the leg or knee or foot. Similarly, in trial DUR001-302 a total of 225 (60.6%) infections in the dalbavancin group and 237 (64.4%) infections in the comparator group were located on the leg or knee or foot. The most common anatomical sites of ABSSSI observed in DUR001-301 and -302 trials are presented in **Table 11**.

Table 11: Anatomical Sites of ABSSSI Infections in the ITT population in DUR001-301 and DUR001-302 Trials

	DUR001-301		DUR001-302	
	Dalbavancin N=288 n (%)	Comparator N=285 n (%)	Dalbavancin N=371 n (%)	Comparator N=368 n (%)
Face/Head/Neck	9 (3.1)	8 (2.8)	18 (4.8)	16 (4.3)
Chest	7 (2.4)	5 (1.8)	5 (1.3)	12 (3.3)
Abdomen	13 (4.5)	11 (3.9)	16 (4.3)	20 (5.4)
Shoulder	3 (1.0)	2 (0.7)	5 (1.3)	3 (0.8)
Axillary	4 (1.4)	8 (2.8)	4 (1.1)	5 (1.4)
Hand	22 (7.6)	20 (7)	11 (3)	11 (3)
Arm	58 (20.1)	71 (24.9)	74 (19.9)	58 (15.8)
Foot	18 (6.3)	13 (4.6)	34 (9.2)	36 (9.8)
Leg	120 (41.7)	113 (39.6)	177 (47.7)	178 (48.4)
Groin	3 (1.0)	5 (1.8)	7 (1.9)	4 (1.1)
Knee	7 (2.4)	18 (6.3)	14 (3.8)	23 (6.3)
Buttock	31 (10.8)	26 (9.1)	21 (5.7)	34 (9.2)
Back	6 (2.1)	5 (1.8)	9 (2.4)	5 (1.4)

The infection can occur on multiple contiguous anatomical sites
Source: modified from Tables 14.2.4.1, clinical study reports DUR001-301 and DUR001-302.

Baseline infection area measurements were provided for 284 subjects in each of the dalbavancin and comparator treatment groups in trial DUR001-301 and for 368 subjects

in each of the dalbavancin and comparator treatment groups in trial DUR001-302, **Table 12**. Of note, in trial DUR001-301 two subjects with major abscesses in the dalbavancin treatment group had an area of infection lower than that required per protocol (minimal area of 75 cm^2); one subject had an area of 25.6 cm^2 and another of 34.2 cm^2. The subjects were considered clinical responders for the primary endpoint but were excluded from the CE-EOT population.

Table 12: Infection Area Baseline Measurements in DUR001-301 and DUR-302 Trials (ITT population)

	DUR001-301		DUR001-302	
Area (cm^2) [a]	Dalbavancin N=288 n (%)	Comparator N=285 n (%)	Dalbavancin N=371 n (%)	Comparator N=368 n (%)
All Infection Types	n = 284	n = 284	n =368	n =368
Mean	498	533	512	580
Median	333	368	313.5	362
Min, max	25.6, 3400	78,3675	85, 5100	72, 3922
Cellulitis	n = 154	n = 146	n = 197	n = 202
Mean	614	671	674.5	722
Median	348.5	496	452	466
Min, max	76.5, 3400	81, 3675	85, 5100	72, 3922
Major Abscess	n = 70	n = 86	n = 90	n = 87
Mean	351	329	311	353
Median	320	315	278	252.5
Min, max	25.6, 1390	88, 1456	110, 1007.5	80, 1813
Wound Infection	n = 60	n = 52	n = 81	n = 79
Mean	374	480	342	465
Median	352	357	269	300
Min, max	84, 1382.5	78, 2820	88, 2006	90, 2471

[a] Area was defined as the longest length x the widest perpendicular width; for trial DUR001-302 the area of infection was specified as the area of erythema.
Source: Tables 11.6 in DUR001-301 and DUR001-302 Clinical Study Reports

The incidence of systemic signs of infection at study entry is provided in **Table 13**. In both trials and in both treatment arms, approximately 82%-84% of subjects had temperature ≥ 38°C at baseline. Systemic inflammatory response syndrome (SIRS) criteria were met by approximately 61% of subjects in trial DUR001-301 and by approximately 42% of subjects in trial DUR001-302.

Table 13: Systemic Signs of Infections at Study Entry in DUR001-301 and DUR001-302 Trials (ITT Population)

	DUR001-301		DUR001-302	
	Dalbavancin N=288 n (%) [a]	Comparator N=285 n (%)	Dalbavancin N=371 n (%)	Comparator N=368 n (%)
Temperature ≥ 38°C	243 (84.4)	242 (84.9)	306 (82.5%)	310 (84.2)
WBC >12,000 cells/mm^3	98 (34.0)	104 (36.5)	149 (40.2)	146 (39.7)
Bands ≥10%, n/n [a]	63/238 (26.5)	66/244 (27.0)	48/241 (19.9)	42/234 (17.9)
Temperature ≥ 38°C and either WBC >12,000 cells/mm^3 or Bands ≥10%	96/288 (33.3)	104/285 (36.5)	107/371 (28.8)	103/368 (28)
SIRS criteria are met [b]	175 (60.7)	175 (61.4)	157 (42.3)	161 (43.7)

[a] Percentages for bands was based on non-missing data
[b] SIRS – systemic inflammatory response syndrome; meeting SIRS criteria is defined as having 2 or more of the following: temperature <36°C or >38°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute, or WBC count <4,000 cells/mm^3 or >12,000 cells/mm^3 or >10% bands.
Source: modified from Tables 11.8, clinical study reports DUR001-301 and DUR001-302.

Greater than 70% of subjects in DUR001-301 and DUR001-302 trials had ABSSSI specimens obtained, **Table 14**.

Table 14: ABSSSI Specimens Obtained in DUR001-301 and DUR001-302 Trials

	DUR001-301		DUR001-302	
	Dalbavancin N=288 n (%)	Comparator N=285 n (%)	Dalbavancin N=371 n (%)	Comparator N=368 n (%)
Subjects with ABSSI specimen obtained	216 (75)	222 (77.9)	267 (72.0)	265 (72.0)
Total number of specimens	221	230	274	275
Type of specimens collected				
Needle aspirate	106/221 (48.0)	106/230 (46.1)	130/274 (47.4)	140/275 (50.9)
Biopsy	34/221 (15.4)	38/230 (16.5)	43/274 (15.7)	35/275 (12.7)
Swab	48/221 (21.7)	51/230 (22.2)	65/274 (23.7)	55/275 (20.0)
Other	29/221 (13.1)	34/230 (14.8)	33/274 (12.0)	42/275 (15.3)
Local laboratory culture results				
Positive for pathogen	170/221 (76.9)	179/230 (77.8)	211/274 (77.0)	215/275 (78.2)
No growth/contaminant	46/221 (20.8)	47/230 (20.4)	44/274 (16.1)	44/275 (16.0)
No culture performed	5/221 (2.3)	4/230 (1.7)	19/274 (6.9)	16/275 (5.8)

Source: modified from Tables 11.10, clinical study reports DUR001-301 and DUR001-302.

In the DUR001-301 trial, a total of 153/288 (53.1%) subjects in the dalbavancin arm and 155/285 (54.4%) subjects in the comparator arm had at least 1 Gram-positive ABSSSI pathogen isolated at baseline from a blood culture or from a culture from the primary

ABSSSI site as shown in **Table 15**. In trial DUR001-302, a total of 184/371 (49.6%) subjects in the dalbavancin and 174/368 (47.3%) subjects in the comparator arm had at least 1 Gram-positive ABSSSI pathogen isolated at baseline. Overall, *S. aureus* constituted about 77% of all isolates and methicillin-resistant *S. aureus* accounted for about 24% of all isolates.

Table 15: Baseline ABSSSI Pathogens (ITT population)

	DUR001-301		DUR001-302	
	Dalbavancin	Comparator	Dalbavancin	Comparator
Intent-to-Treat	N=288	N=285	N=371	N=368
Micro-ITT [a]	153 (100.0)	155 (100.0)	184 (100.0)	174 (100.0)
Subjects with ≥ 1 Gram-positive aerobe	146 (95.4)	152 (98.1)	174 (94.6)	161 (92.5)
Subjects with *Staphylococcus aureus* [b]	123 (80.4)	127 (81.9)	135 (73.4)	127 (73)
MRSA	41 (26.8)	42 (27.1)	47 (25.5)	27 (15.5)
MSSA	78 (51.0)	84 (54.2)	84 (45.7)	95 (54.6)
S. aureus (non-specified)	5 (3.3)	9 (5.8)	6 (3.3)	8 (4.6)
Streptococcus pyogenes	12 (7.8)	14 (9.0)	25 (13.6)	22 (12.6)
Streptococcus constellatus	5 (3.3)	8 (5.2)	10 (5.4)	8 (4.6)
Enterococcus faecalis	3 (2.0)	5 (3.2)	9 (4.9)	8 (4.6)
Streptococcus agalactiae	3 (2.0)	6 (3.9)	9 (4.9)	8 (4.6)
Streptococcus intermedius	0	3 (1.9)	6 (3.3)	4 (2.3)
Streptococcus viridans group	2 (1.3)	3 (1.9)	5 (2.7)	3 (1.7)
Streptococcus anginosus	2 (1.3)	3 (1.9)	4 (2.2)	1 (0.6)
Streptococcus dysgalactiae	0	0	3 (1.6)	1 (0.6)
Streptococcus Group C	5 (3.3)	2 (1.3)	0	3 (1.7)
Number of patients with at least 1 Gram-negative pathogen (aerobes)	17 (11.1)	17 (11.0)	24 (13.0)	30 (17.2)

[a] Microbiological intent-to-treat (micro-ITT) population – all subjects in the ITT population with at least 1 Gram-positive bacterial pathogen isolated at baseline from a blood culture or from a culture of a microbiological sample obtained from the primary ABSSSI site from an acceptable source.
[b] A subjects may have more than one *S. aureus* isolate
MRSA – methicillin-resistant *S. aureus*: MSSA – methicillin-sensitive *S. aureus*
Derived from ADPATH analysis datasets for trials DUR001-301 and DUR001-302, submission modules 5.3.5.1.

6.1.3 Subject Disposition

In DUR001-301 and DUR001-302 trials, a total of 659 and 653 subjects were randomized and included in the ITT population in the dalbavancin and vancomycin arm, respectively.

Nine subjects (7 in the dalbavancin and 2 in comparator arm) were randomized to but did not receive study drug and were not included in the Safety population. In trial 301 a

total of 5 subjects (4 in the dalbavancin and 1 in the comparator arm) were not included in the Safety population: 2 subjects withdrew consent prior to dosing, 2 did not meet inclusion/exclusion criteria, and 1 was lost to follow-up prior to initiation of study drug dosing. In trial 302, a total of 4 subjects (3 in the dalbavancin and 1 in the comparator arm) were not included in the safety population: 3 dalbavancin subjects withdrew consent prior to dosing and 1 patient in comparator arm received placebo, but was discontinued from study drug on Day 1 due to AE's of flushing, nausea, bitter taste, hypotension and vertigo.

Subject disposition in trials DUR001-301 and -302 is presented in **Table 16**. It has to be noted that categories of study drug discontinuations and study dropouts are not mutually exclusive. A subject could stop study drug but still be followed for safety, meaning that a subject could discontinue study drug but complete the study. At the same time, a subject could receive a planned study treatment but withdraw from the study after that. The table presents data on study completion regardless whether subjects discontinued study drug or not. Study drug discontinuations are discussed in section 7.3.3 Dropouts and/or Discontinuations.

The numbers of subjects who discontinued the trials were similar in the dalbavancin and comparator arms, 66 (10%) and 63 (9.6%), respectively. The main reason for discontinuation was a loss to follow-up, 38 (5.8%) and 29 (4.4%) in the dalbavancin and comparator arms, respectively. There were 8 (1.2%) and 1 (0.2%) deaths in the comparator and dalbavancin arm, respectively. A total of 12 and 11 subjects were reported to discontinue the study under the disposition category of "other." The verbatim terms used under this category were reviewed. Although some subjects may have been categorized more precisely, for instance as "lost to follow-up" instead of "other", no evident imbalances between study arms were found.

Table 16: Study Dropouts in DUR001-301 and 302 trials

	Dalbavancin		Vancomycin	
	Subject Count	%	Subject Count	%
Informed consent obtained	659	100.0	653	100.0
Randomized	659	100	653	100
No study drug given	7	1.1	2	0.3
Received at least one dose of study drug	652	98.9	651	99.7
Completed study	593	90	589	90.2
Did not complete study	66	10	63	9.6
Lost to follow-up	38	5.8	29	4.4
Withdrawal by subject	15	2.3	15	2.3
Death	1	0.2	8	1.2
Other	12	1.8	11	1.7

Table 17 presents the number of subjects in analysis populations in DUR001-301 and DUR001-302 trials.

Table 17: Number of Subjects in Analysis Populations in DUR001 and DUR002 trials

	DUR001-301		DUR001-302		DUR001-301 & -302		
Analysis Population	**DALB n (%)**	**Compar. n (%)**	**DALB n (%)**	**Compar. n (%)**	**DALB n (%)**	**Compar. n (%)**	**Total n (%)**
ITT	288 (100)	285 (100)	371 (100)	368 (100)	659 (100)	653 (100)	1312 (100)
Safety	284 (98.6)	284 (99.6)	368 (99.2)	367 (99.7)	652 (98.9)	651 (99.7)	1303 (99.3)
MicroITT	153 (53.1)	155 (54.4)	184 (49.6)	174 (47.3)	337 (51.1)	329 (50.4)	666 (50.8)
CE-EOT	246 (85.4)	243 (85.3)	324 (87.3)	302 (82.1)	570 (86.5)	545 (83.5)	1115 (85)
CE-SFU	226 (78.5)	229 (80.4)	294 (79.2)	272 (73.9)	520 (78.9)	501 (76.7)	1021 (77.8)
CE-LFU	219 (76.0)	212 (74.4)	280 (75.5)	267 (72.6)	499 (75.7)	479 (73.3)	978 (74.5)
ME	123 (42.7)	128 (44.9)	156 (42.0)	131 (35.6)	279 (42.3)	259 (39.7)	538 (41.0)
ME-SFU	110 (38.2)	118 (41.4)	141 (38.0)	120 (32.6)	251 (38.1)	238 (36.4)	489 (37.3)

CE-LFU = clinically evaluable at the long-term follow-up visit; CE-SFU = clinically evaluable at the short-term follow-up visit; ITT = intent-to-treat; ME = microbiologically evaluable; ME-SFU = microbiologically evaluable at the short-term follow-up visit; microITT = microbiological intent-to-treat; DALB- dalbavancin; Compar. – comparator

6.1.4 Analysis of Primary Endpoint

In both clinical trials dalbavancin has comparable clinical efficacy to the comparator regimen for the primary efficacy outcome measure of cessation of spread of lesion and the absence of fever at 48 to 72 hours, Table 18. In trial DUR001-301, a total of 240 (83.3%) subjects in the dalbavancin and 233 (81.8%) in the comparator group were early clinical responders (95% CI, -4.6, 7.9). In trial DUR001-302 a total of 285 (76.8%) subjects in the dalbavancin and 288 (78.3%) in the comparator arm were early clinical responders (95% CI, -7.4, 4.6). Since the lower bound of the 95% confidence interval for the treatment difference was above -10% (i.e., -4.6% in trial DUR001-301 and -7.4% in trial DUR001-302), both trials met their primary objectives.

Table 18: Primary Efficacy Analysis in Trials DUR001-301 and DUR001-302: Early response at 48–72 hours in the ITT population

	Dalbavancin n/N (%)	Vancomycin/Linezolid, n/N (%)	Difference (95% CI)
DUR001-301	240/288 (83.3%)	233/285 (81.8%)	1.5% (-4.6, 7.9)
DUR001-302	285/371 (76.8%)	288/368 (78.3%)	-1.5% (-7.4, 4.6)

ITT - All randomized patients regardless of receiving study drug. In addition to patients with missing measurements, patients who used non-study systemic antibacterials or died within 48-72 hours were counted as non-responders.

Early clinical response by ABSSSI type in the ITT population is presented in **Table 19**. In trial DUR001-301, there were more early responders with cellulitis in the dalbavancin arm (85.3%) as compared to the comparator arm (78.9%) and fewer responders with abscess, 80.6% and 84.9%, and wound infection, 81.7% and 84.6%, respectively.

The rate of early clinical response among subjects with different ABSSSI type was comparable in trial DUR001-301, **Table 19**. In trial DUR001-302, clinical success rates at 48-72 hours were higher in subjects with abscesses. Treatment differences favored dalbavancin in patients with cellulitis (trial DUR001-301) and the comparator for patients with major abscess (trials DUR001-301 and -302).

Table 19: Clinical Response at 48-72 Hours by ABSSSI Type (ITT Population)

	DUR001-301		DUR001-302	
	Dalbavancin N=288	Comparator N=285	Dalbavancin N= 371	Comparator N= 368
Cellulitis	n=156	n=147	n=198	n=202
Clinical Responder	133 (85.3)	116 (78.9)	148 (74.7)	153 (75.7)
Difference (95% CI)	6.4 (-2.3, 15.1)		-1.0 (-9.5, 7.5)	
Abscess	n=72	n=86	n=91	n=87
Clinical Responder	58 (80.6)	73 (84.9)	75 (82.4)	76 (87.4)
Difference (95% CI)	-4.3 (-16.8, 7.5)		-4.9 (-15.7, 5.9)	
Wound Infection	n=60	n=52	n=82	n=79
Clinical Responder	49 (81.7)	44 (84.6)	62 (75.6)	59 (74.7)
Difference (95% CI)	-2.9 (-17.0, 11.7)		0.9 (-12.5, 14.4)	

Source: Tables 14.6.1.6 in clinical study reports DUR001-301 and -302

Clinical response rates at 48 to 72 hours by presence or absence of fever at baseline and by geographic region for trials DUR001-301 and DUR001-302 are presented in Table 20 and Table 21, respectively. In both trials, clinical response rates were higher among patients with fever at baseline. With regard to geographic region, clinical response rates were inconsistent between trial DUR001-301 and -302. In trial DUR001-301 in both treatment arms, somewhat lower rates were observed in North America as compared to the rest of the world; whereas higher rates were observed in trial DUR001-302.

Table 20: Clinical Response Rates at 48-72 hours by Presence of Fever and Geographic Region in Trial DUR001-301 (ITT)			
Stratification Variables	Dalbavancin (N=288) n/N* (%)	Comparator (N=285) n/N* (%)	Difference (95% CI)
Fever at Baseline			
Febrile	200/236 (84.7)	200/235 (85.1)	-0.4 (-6.9. 6.2)
Afebrile	40/52 (76.9)	33/50 (66.0)	10.9 (-6.7, 28.2)
Region			
N. America	100/123 (81.3)	93/121 (76.9)	4.4 (-5.9, 14.7)
Rest of World	140/165 (84.8)	140/164 (85.4)	-0.6 (-8.4, 7.3)
Source: Tables 14.6.1.3 and 14.6.1.5 in DUR001-301 clinical study report			

Table 21: Clinical Response Rates at 48-72 hours by Presence of Fever and Geographic Region in Trial DUR001-302 (ITT)			
Stratification Variables	Dalbavancin (N=371) n/N* (%)	Comparator (N=368) n/N* (%)	Difference (95% CI)[1]
Fever at Baseline			
Febrile	239/303 (78.9)	237/303 (78.2)	0.7 (-5.9, 7.2)
Afebrile	46/68 (67.6)	51/65 (78.5)	-10.9 (-25.6, 4.4)
Region			
N. America	96/115 (83.5)	96/114 (84.2)	-0.7 (-10.5, 9.0)
Rest of World	189/256 (73.8)	192/254 (75.6)	-1.8 (-9.3, 5.8)
Source: Tables 14.6.1.3 and 14.6.1.5 in DUR001-302 clinical study report			

6.1.5 Analysis of Secondary Endpoints

Clinical response rates at 48-72 hours defined as a ≥20% reduction in lesion area from baseline (without regard to fever) was considered a key secondary endpoint by the FDA. Both trials satisfied this secondary endpoint, **Table 22**. Overall response rates were approximately 6% to 9% higher in both trials as compared to the primary efficacy endpoint of cessation of spread of lesion and the absence of fever at 48 to 72 hours.

Table 22: Key Secondary Endpoint in Trials DUR001-301 and DUR001-302 (ITT)			
	Dalbavancin n/N (%)	Vancomycin/Linezolid n/N (%)	Difference (95% CI)
≥ 20% Reduction in Lesion Area from Baseline at 48–72 hours			
DUR001-301	259/288 (89.9)	259/285 (90.9)	-1% (-5.7, 4.0)
DUR001-302	325/371 (87.6)	316/368 (85.9)	1.7% (-3.2, 6.7)
ITT = All randomized patients, regardless of receiving study drug. In addition to patients with missing measurements, patients who used non-study systemic antibacterial drugs or died within 48-72 hours were counted as non-responders.			

The analyses of secondary endpoints of clinical status at EOT (success/failure) in the ITT and CE-EOT populations and clinical status at SFU in the ITT population are presented in **Table 23**. These endpoints served to evaluate the maintenance of the clinical response achieved at 48-72 hours at later timepoints. No pre-specified NI margin was determined for these endpoints.

In trial DUR001-301, the response rates at these later endpoints were lower in the dalbavancin than in the comparator arm. In the ITT population, clinical success rates at EOT were 81.3% and 86.7% in the dalbavancin and comparator arms, respectively, a difference of -5.4%, 95% CI: (-11.5, 0.6). Similar differences were observed at the SFU visit where the clinical response rate was 83.7% and 88.1% in the dalbavancin and comparator arms, respectively, a difference of -4.4%, 95% CI: (-10.2, 1.3).

In contrast, in trial DUR001-302, clinical response rates at later endpoints were somewhat higher in the dalbavancin than in the comparator arms. At the EOT visit, clinical response rates were 88.7% and 85.3% in the dalbavancin and comparator arms, respectively, with a difference (95% CI) of 3.4 (-1.5, 8.3). At the SFU visit, clinical response rates were 88.1% and 84.5% in the dalbavancin and comparator arm, respectively, with a difference (95% CI) of 3.6% (-1.3, 8.7).

Table 23: Secondary Clinical Efficacy Endpoint Analysis in Trials DUR001-301 and DUR001-302			
Endpoint Definition	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)
DUR001-301			
Clinical Success at EOT (ITT)	234/288 (81.3)	247/285 (86.7)	-5.4 (-11.5, 0.6)
Clinical Success at EOT (CE)	212/246 (86.2)	222/243 (91.4)	-5.2 (-10.9, 0.4)
Clinical Success at SFU (ITT)	241/288 (83.7)	251/285 (88.1)	-4.4 (-10.2, 1.3)
DUR001-302			
Clinical Success at EOT (ITT)	329/371 (88.7)	314/368 (85.3)	3.4 (-1.5, 8.3)
Clinical Success at EOT (CE)	303/324 (93.5)	279/302 (92.4)	1.1 (-2.9, 5.3)
Clinical Success at SFU (ITT)	327/371 (88.1)	311/368 (84.5)	3.6% (-1.3, 8.7)
EOT – end of treatment (Day 14-15); CE - Clinically evaluable; ITT - all randomized patients, regardless of whether or not they received study medication; SFU – short-term follow-up (Day 26-30)			

The analyses of concordance of clinical response at 48-72 hours with clinical status at EOT are presented in **Table 24**. In the DUR001-301 trial, 14.2% of clinical responders at 48-72 hours patients in the dalbavancin arm became clinical failures at EOT as compared to 8.6% in the comparator arm. In the DUR001-302 trial, slightly lower failure rates were observed among the responders at EOT in the dalbavancin arm, 22/285 (7.7%) versus 28/288 (9.7%) for the comparator arm.

Table 24: Concordance Analysis - Responder/Non-Responders at 48-72 Hours *with* Clinical Success/Failure at EOT in the ITT Population

	Dalbavancin	Comparator	Dalbavancin	Comparator
Trial DUR001-301	Responders (N=240)	Responders (N=233)	Non-Responders (N=48)	Non-Responders (N=52)
Clinical Success at EOT, n (%)	206 (85.8)	213 (91.4)	28 (58.3)	34 (65.4)
Clinical Failure at EOT, n (%)	34 (14.2)	20 (8.6)	20 (41.7)	18 (34.6)
Trial DUR001-302	Responders (N=285)	Responders (N=288)	Non-Responders (N=86)	Non-Responders (N=80)
Clinical success at EOT, n (%)	263 (92.3)	260 (90.3)	66 (76.7)	54 (67.5)
Clinical failure at EOT, n (%)	22 (7.7%)	28 (9.7)	20 (23.3)	26 (32.5)

The types of ABSSSI in subjects with clinical failures at EOT that were responders at 48-72 hours are presented in **Table 25**. In trial DUR001-301, the majority of early responders who were then determined to be clinical failures at EOT had wound infection; in trial DUR001-302, cellulitis was the most common type of infection in this group of subjects.

Table 25: ABSSSI Type in Subjects with Clinical Failures at EOT that were Responders at 48-72 hours

	DUR001-301		DUR001-302	
	Dalbavancin n = 34	Comparator n = 20	Dalbavancin n = 22	Comparator n = 28
Cellulitis	13 (38.2%)	5 (25%)	12 (54.5%)	21 (75%)
Major abscess	5 (14.7%)	5 (25%)	5 (22.7)	4 (14.3%)
Wound infection	16 (47.1%)	10 (50%)	5 (22.7%)	3 (10.7%)

The reasons for failures in subjects who responded at 48-72 hours but failed at EOT were further evaluated and are presented in **Table 24**. In the DUR001-301 trial, where the imbalance between dalbavancin and comparator in terms of the maintenance of clinical response was most noticeable, a total of 34 and 20 early responders in the

dalbavancin and comparator arms, respectively, became clinical failures at EOT. These included 8 dalbavancin and 6 comparator subjects that were declared to have an indeterminate outcome (these subjects lacked required data on lesion measurements and infection signs). Overall the receipt of non-study antibacterial agents for ABSSSI and incomplete resolution of local signs of infection accounted for the greater number of failures at EOT among dalbavancin subjects.

Table 26: Reason for Clinical Failure at EOT among Responders at 48-72 hours

	DUR001-301		DUR001-302	
	Dalbavancin n = 34	Comparator n = 20	Dalbavancin n = 22	Comparator n = 28
Indeterminate	**8**	**6**	**5**	**10**
No EOT Visit, Missing all Measurement Data	8	6	3	4
Missing Temperature Measurement Only	0	0	1	5
Missing Lesion Measurement Only	0	0	1	1
Clinical Failure	**26**	**14**	**17**	**18**
Lesion Size at EOT is not Decreased from Baseline	4	0	1	1
Temperature at EOT >37.6C	0	0	1	0
Local Signs of Infection Have not Resolved	22	13	11	11
Received a Non-Study Systemic Antibacterial Treatment for ABSSSI	6	1	3	3
Death	0	1	0	0
Surgical Intervention before EOT	1	0	7	5

Another measure of clinical response is the time to the point when the subjects met criteria for switching to oral therapy and time to the point when the investigator felt that no further antibacterial therapy was needed. Although the treatment in the dalbavancin arm cannot be exactly “stopped” because the subjects continues to be exposed to the drug, in these double-dummy double-blinded trials the time on IV therapy and time of total days on study drug allow estimating clinical response. No difference was observed between treatment arms with regard timing of oral switch or total duration of study treatment, **Table 27**.

Table 27: Time to Oral Switch and Total Duration of Study Treatment in DUR001-301 and DUR001-302 trials (ITT population)				
	DUR001-301		**DUR001-302**	
	Dalbavancin N=288	**Comparator N=285**	**Dalbavancin N=371**	**Comparator N=368**
Time of the switching to oral therapy (the mean total days of IV therapy)[a]	4.8	4.8	3.8	3.8
The mean total days on study drug (IV and oral)[b]	10.6	11.0	11.1	11.1
ITT - intent-to-treat [a] Placebo in the dalbavancin arm and vancomycin in the comparator arm [b] Placebo in the dalbavancin arm and linezolid in the comparator arm				

6.1.7 Subpopulations

In addition to subgroup analyses presented in section 6.1.5 Analysis of Secondary Endpoints, clinical response was compared in subjects ≥ 65 years and those < 65 years, Table 28. The efficacy of dalbavancin was similar to comparator regardless of age.

Table 28: Clinical Response at 48-72 hours by Age				
	DUR001-301		DUR001-302	
Age (years)	Dalbavancin n/N (%)	Comparator n/N (%)	Dalbavancin n/N (%)	Comparator n/N (%)
< 65	208/251 (82.9%)	200/242 (82.6%)	228/301 (75.7%)	222/287 (77.4%)
≥ 65	32/37 (86.5%)	33/43 (76.7%)	57/70 (81.4%)	66/81 (81.5%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing regimen of dalbavancin was selected based on the results of a phase 2 dose response trial VER001-5, titled “A Phase 2, Pilot, Randomized, Open-Label, Multi-Center Study to Evaluate the Safety and Efficacy of Dalbavancin Versus Investigator/Physician-Designated Comparator in Skin and Soft Tissue Infection (SSTI).” The trial was conducted in July 2001 – June 2002.

The trial included 3 arms:

1. 1100 mg Dalbavancin IV on Day 1
2. 1000 mg Dalbavancin on Day 1 and 500 mg Dalbavancin on Day 8
3. Comparator at standard doses Days 1-21

Treatment duration was ≥ 7 days and ≤ 21 days. The primary efficacy endpoint was the Investigator's assessment of clinical response in the clinically evaluable population at the follow-up visit, i.e. 14 days +/-2d after the End-of-Treatment (EOT). The EOT was defined as Day 10 for Study Arm 1 and Day 20 for Study Arm 2.

Subjects with the following characteristics of SSTI were included:

- SSTI was suspected to be caused by only Gram-positive cocci, based on Gram stain or culture results.
- Involved deeper soft tissue and/or required significant surgical intervention (such as a major abscess, infected ulcer, major burn [≤ 20% body surface area], or deep and extensive cellulitis).
- Presented with at least two of the following symptoms:
    - drainage/discharge
    - erythema
    - fluctuance
    - heat/localized warmth
    - pain/tenderness to palpation
    - swelling/induration.

Key exclusion criteria included previous antibiotic treatment for SSTI for more than 24 hours within 7 days of study entry unless the pathogen showed drug resistance or the treatment failed (defined as no clinical improvement after 3 days of treatment).

A clinical assessment of the SSTI was performed at baseline, EOT, and 14 ± 2 days after EOT (follow-up). Visit windows were as follows:

Baseline – within 2 days before study start (48 hours)
EOT – +/- 1 day (24 hours)

- Study Arm 1 = Day 10
- Study Arm 2 = Day 20
- Study Arm 3 = Day 7-21 (day of last dose given to patients)

Follow-up – +/- 2 days (48 hours)

- Study Arm 1 = Day 24
- Study Arm 2 = Day 34
- Study Arm 3 = Day 21-35 (2 weeks after EOT, depending on day of last dose given).

Analysis populations were as follows:

Intent-to-Treat Population: all randomized patients who received any amount of study drug, Intent-to-Treat (ITT), analyzed for safety.
Microbiological Intent-to-Treat Population: all patients in the ITT population who had a documented Gram-positive pathogen at baseline.
Clinically Evaluable (at EOT and Follow-Up):

- To be clinically evaluable at the EOT visit, patients had SSTI at baseline and did not violate the protocol in such a way that precluded clinical evaluability.
- To be clinically evaluable at the follow-up visit, patients also must have returned for a follow-up visit (unless failure at EOT).

Microbiologically Evaluable (at EOT and Follow-Up): patients that were clinically evaluable at either EOT or follow-up and had a Gram-positive pathogen isolated from the SSTI site at baseline.

Distribution of subjects in trial populations is presented in **Table 29**.

Table 29: Analysis Populations in Study VER001-5

	Arm 1	Arm 2	Arm 3
ITT	N=20	N=21 [a]	N=21
Microbiological ITT	16/20	17/21	14/21
Clinically evaluable at EOT	16/20	17/21	21/21
Clinically evaluable at follow-up	13/20	17/21	21/21
Microbiologically evaluable at EOT	13/20	11/21	14/21
Microbiologically evaluable at follow-up	11/20	11/21	14/21

[a] One subject received only 1000 mg dalbavancin on Day 1
Note: In Study Arm 3, mean duration of comparator treatment was 15 days.

Clinical response rates in the clinically evaluable population at follow-up, the primary efficacy endpoint, were higher in study arm 2 (2 weekly doses of dalbavancin), 94.1%, as compared to arm 1, single dose of dalbavancin, 61.5%, and to arm 3 (comparators), 76.2%, **Table 30**.

Table 30: Clinical Response in study VER001-5 (Clinically Evaluable Population at Follow-Up

Response	Study Arm 1 n/N (%)	Study Arm 2 n/N (%)	Study Arm 3 n/N (%)
Success	8/13 (61.5%)	16/17 (94.1)	16/21 (76.2)
Cure	6/13 (46.2%)	16/17 (94.1)	12/21 (57.1)
Improvement	2/13 (15.4)	0/17	4/21 (19)
Failure	5/13 (38.5)	1/17 (5.9)	5/21 (23.8)

n – number of patients with response; N – number of patients who were evaluated

As a result, a regimen of 2 weekly doses of dalbavancin was selected for subsequent trials.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The aspects of efficacy analyses related to the maintenance of clinical response are discussed in section 6.1.5 Analysis of Secondary Endpoints.

6.1.10 Additional Efficacy Issues/Analyses

Outcomes in Subjects with Bacteremia

In DUR001-301 and DUR001-302 trials, the number of subjects with bacteremia due to Gram-positive pathogens was 28 (4.2%) in the dalbavancin and 17 (2.6%) in the comparator groups. The most frequently isolated pathogen from baseline blood cultures was *S. aureus*, 11 in the dalbavancin and 9 in the comparator groups. All isolate were MSSA with the exception of one MRSA isolate in each treatment group. Other pathogens mostly included various streptococci and coagulase-negative staphylococci.

The rate of clinical response at 48-72 hours in subjects with Gram-positive anaerobes was somewhat lower in the dalbavancin arm as compared to the comparator arm, **Table 31**. A total of 7 (25%) out of 28 dalbavancin subjects as compared with 2 (11.8%) out of 17 comparator subjects with Gram-positive aerobes bacteremia at baseline were clinical non-responders at 48-72 hours of treatment.

Table 31: Clinical Response at 48-72 hours in Patients with Bacteremia due to Gram-positive Aerobes at Baseline (ITT population)

	DUR001-301		DUR001-302	
	Dalbavancin N=288	Comparator N=285	Dalbavancin N=371	Comparator N=368
Total Gram-positive aerobes	8	6	20	11
	n (%)	n (%)	n (%)	n (%)
Clinical responder	6 (75)	5 (83.3)	15 (75)	10 (90.9)
Clinical non-responder	2 (25)	1 (16.7)	5 (25)	1 (9.1)

Source: Table 14.6.1.10 in DUR001-301 study report and Table 14.6.2.14 in DUR001-302 study report

The lower rate of clinical response in subjects with bacteremia does not seem to be associated with the persistence of bacteremia, however. On the contrary, the persistence of bacteremia has not been documented in any of dalbavancin-treated subjects but in 2 subjects in the comparator arms. Clearance of bacteremia is presented in **Table 32**.

Table 32: Clearance of Bacteremia due to Gram-positive Aerobes at the End-of-Treatment Visit (Micro-ITT Population)

	DUR001-301		DUR001-302	
	Dalbavancin N=153	**Comparator N=155**	**Dalbavancin N=184**	**Comparator N=174**
Total Gram-positive aerobes	**8**	**6**	**20**	**11**
	n (%)	n (%)	n (%)	n (%)
Documented clearance of bacteremia	5 (62.5)	3 (50)	17 (85)	9 (81.8)
Documented persistent bacteremia	0	1 (16.7)	0	1 (9.1) [a]
No follow-up blood culture	3 (37.5)	2 (33.3)	3 (15)	1 (9.1)
MRSA	1	0	0	1
Documented clearance of bacteremia	1 (100)	0	0	1 (100)
Documented persistent bacteremia	0	0	0	0
No follow-up blood culture	0	0	0	0
MSSA	3	3	7	5
Documented clearance of bacteremia	2 (66.7)	2 (66.7)	7 (100)	5 (100)
Documented persistent bacteremia	0	1 (33.3)	0	0
No follow-up blood culture	1 (33.3)	0	0	0
Streptococcus agalactiae	3	0	2	1
Documented clearance of bacteremia	2 (66.7)	0	1 (50)	1 (100)
Documented persistent bacteremia	0	0	0	0
No follow-up blood culture	1 (33.3)	0	1 (50)	0
Streptococcus pyogenes	1	0	3	1
Documented clearance of bacteremia	0	0	1 (33.3)	0
Documented persistent bacteremia	0	0	0	0
No follow-up blood culture	1 (33.3)	0	2 (66.7)	1 (100)

Micro-ITT - microbiological intent-to-treat; MRSA - methicillin-resistant *Staphylococcus aureus*; MSSA - methicillin-sensitive *Staphylococcus aureus*
[a] Subjects DUR001302-876-416 with *Enterococcus faecalis*
Source: Table 11.51 in DUR001-301 study report and Table 11.49 in DUR001-302 study report

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review focuses on two new phase 3 trials (DUR001-301 and DUR001-302). If deemed necessary, aggregate safety analyses of all seven phase 2 and 3 trials were conducted, **Table 33**. In addition, safety analysis of selected Phase 1 trials (e.g. a thorough QT study) was conducted. Phase 1 safety datasets were searched for adverse events of interest, for instance liver function test abnormalities.

Table 33: Phase 2 and Phase 3 Dalbavancin Trials (Safety Population)

Trial	Phase	Indication	Design	Dalbavancin	Comparator
VER001-4	2	Catheter-Related Bloodstream Infections	Open-label	40	34
VER001-5	2	Complicated Skin and Soft Tissue Infection (SSSI)	Open-label	41	21
VER001-8	3	Uncomplicated SSSI	Double-blind [a]	367	186
VER001-9	3	Complicated SSSI	Double-blind [a]	571	283
VER001-16	3	Complicated or Uncomplicated SSSI with suspected or confirmed MRSA	Open-label [a]	107	49
DUR001-301	3	Acute Bacterial Skin and Skin Structure Infections	Double-blind	284	284
DUR001-302	3	Acute Bacterial Skin and Skin Structure Infections	Double-blind	368	367
Total				**1778**	**1224**

[a] randomization ratio of 2:1

Safety was evaluated in the safety population that included subjects who received any dose of study drug. For trials DUR001-301 and -302, the safety population differs from ITT population. The latter was defined as all randomized subjects whether or not they received study drug. As described in Section 6.1.3 Subject Disposition a total of 9 subjects, 7 in the dalbavancin and 2 in vancomycin/linezolid arm were randomized but did not receive study drug and were not included in the safety population. For the legacy trials the ITT population was defined as subjects who received at least one dose of study drug and therefore, was the same as the safety population.

A phase 1 study DUR001-104 is described in 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound section. This was an open-label, multiple-dose, safety and PK study of increasing dosing durations in 18 healthy volunteers. All subjects received 1000 mg dalbavancin at Day 1 and weekly doses of 500 mg of dalbavancin for up to 3, 5, or 7 additional weeks (up 4500 mg total exposure).

7.1.2 Categorization of Adverse Events

Treatment-emergent AEs, defined as any adverse experience that occurred during or after the onset of study drug administration, whether or not it was considered study drug-related, were summarized. Adverse events were mapped to Preferred Terms (PTs) using the MedDRA Version 14.0. All AEs are organized by System Organ Class (SOC) and preferred terms (PT). Events that have the potential to be coded into several categories were checked manually as well as analyzed by creating Standardized MedDRA Queries (SMQs).

Safety analyses were conducted by reviewing sponsor's safety reviews and summaries and searching and querying submitted SDTM and ADaM datasets. In addition, safety datasets were analyzed with the MedDRA-Based Adverse Event Diagnostics (MAED), an adverse event analysis tool. These analyses were conducted for all levels of the MedDRA hierarchy but finally preferred terms were included in the review. In addition, Standardized MedDRA Queries (SMQs)—narrow, broad, and algorithm were created. Safety analyses were also conducted using the JReview, another software tool for analyses of adverse events.

The adverse events verbatim terms were coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. The quality of coding was evaluated by comparing reported terms with respective selected preferred terms. The coding was found to be acceptable.

When deemed appropriate, the reviewer conducted searches for AEs across relevant SOCs, for instance for evaluation of the incidence of hypersensitivity reactions, adverse events were searched with terms included under the SOC of skin and subcutaneous tissue disorders (e.g. rash), immune system disorders (e.g. anaphylactoid reaction), and blood and lymphatic system disorders (e.g. eosinophilia).

The AEs reported under the SOC "Investigations" were analyzed during analyses of AEs related to a relevant organ system. Of note, the majority of adverse events reported under the SOC "Investigations" are related to liver function test abnormalities. Thus, a total of 50 out 85 and 31 out of 59 adverse events reported under this SOC represented liver function abnormalities in the dalbavancin and comparator arm, respectively.

The following groups of adverse events were analyzed in detail: Hepatic disorders and Liver Function Tests Abnormalities, Hyperglycemia and Hypoglycemia, Hypersensitivity Reactions, Hematological Abnormalities, Renal Toxicity, and Nervous system disorders.

These events were selected for additional analyses because they were known to occur with glycopeptides, or were reported at a greater rate for dalbavancin in the new or legacy trials.

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

As discussed above, data from two new clinical trials DUR001-301 and -302 were pooled for analysis. In addition, data from all seven phase 2 and 3 trials, namely VER001-4, VER001-5, VER001-8, VER001-9, VER001-16, DUR001-301, and DUR001-302, were pooled for analysis when deemed necessary, **Table 33**.

The pooling of all phase 2 and 3 trials has certain limitations and should be viewed with caution. Two out of 5 legacy trials were phase 2 and three trials were open label. In addition, trials were conducted for various indications and use different comparators. There were important differences in exclusion criteria pertinent to safety assessments, **Table 34**.

Table 34: Selected Differences in Study Population Selection Criteria between Prior Phase 2/3 clinical trials and DUR001-301 and DUR001-302 trials

	Prior Phase 2/3 trials (N=5)	DUR001-301 and -302
Creatinine clearance ≤ 50 mL/min [a]	Excluded	Allowed
Oliguria [b]	Excluded from 3/5 trials	Allowed
Bilirubin > 2x the ULN	Excluded from all but VER001-5	Allowed

[a] ≤ 50 mL/min in VER001-5, VER001-8, and VER001-9; < 50 mL/min in VER001-4 and VER001-16
[b] Oliguria was defined as urine output < 20 cc/hour averaged over 24 hours; subjects with oliguria were excluded from VER001-4, VER001-8, and VER001-9 trials.

7.2 Adequacy of Safety Assessments

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

Because of dalbavancin's pharmacokinetic properties, a single dose of the drug provides a 7-day exposure and the proposed treatment regimen of two injections at day 1 and day 8 provides a 14-day exposure. Therefore, subjects treated with 1 dose of dalbavancin were considered to have been dosed for 7 days and subjects treated with 2 doses of dalbavancin were considered to have been dosed for 14 days.

A total of 2085 subjects received at least one dose of dalbavancin; 1778 subjects received dalbavancin in phase 2 and 3 trials, including 652 subjects in trials DUR001-301 and DUR001-302, **Table 35**.

Table 35: Subjects Receiving ≥ 1 dose of Dalbavancin in Clinical Trials

	Phase 1 trials	Phase 2 Trials	Phase 3 trials *	All phase 2 and 3 trials	DUR001-301 and -302	All clinical trials
No of Trials	14	2	5	7	2	21
Dalbavancin	307	81	1697	1778	652	2085
Comparator	124	55	1169	1224	651	1348
Total	431	136	2866	3002	1303	3433

* Including new phase 3 trials DUR001-301 and -302

The proposed treatment dose of two IV infusions, one on Day 1 and another on Day 8 was received by 27 subjects in phase 1 trials and 1408/1778 (79.2%) subjects in phase 2 and 3 trials, **Table 36**. In trials DUR001-301 and DUR01-302, a total of 620/ 652 (95.1%) subjects received two doses and 32/652 (4.9%) received one dose of dalbavancin.

Table 36: Exposure to Dalbavancin in Phase 2 and 3 Trials

	DUR001-301 and -302 N=652	**Phase 2 and 3 N=1778**
1 dose (Day 1)	32	370
2 doses (Day 1 and 8)	620	1408

1 dose corresponds to a 7-day exposure and 2 doses to a 14-day exposure

Since the prior phase 2 and 3 trials excluded subjects with creatinine clearance < 50 mL/min, no dose adjustments were needed. The majority of the prior phase 2 and 3 trials included a dose regimen of 1000 mg on Day 1 and 500 mg on Day 8. In DUR001-301 and DUR001-302 trials subjects with renal impairment were included and for patients with creatinine clearance <30 mL/min and not on renal dialysis the dalbavancin regimen was 750 mg on Day 1 and 375 mg on Day 8. Overall, in phase 2/3 trials the majority of subjects, 1392/1408, received 1000 mg dalbavancin on Day 1 and 500 mg dalbavancin on Day 8.

In trials DUR001-301 and -302, a total of 48 out of 652 dalbavancin-treated subjects received a total dose of <1500 mg. Sixteen of these 48 patients received 2 doses of dalbavancin; 15 out of these 16 received a reduced first dose of dalbavancin (750 mg) due to underlying renal impairment and 1 patient received in error 500 mg of dalbavancin on Day 1 and on Day 2, **Table 37**.

Table 37: Subjects Who Received a Total Dose of < 1500 mg in DUR001-301 and DUR001-302 Trials (n=48)	
2 Doses	**16**
750 mg and 500 mg *	10
750 mg and 375 mg *	5
500 mg and 500 mg	1
1 Dose	**32**
750 mg	3
1000 mg	29
Total	**48**
* received a reduced dose due to renal impairment	

Out of 15 subjects with renal impairment who received both doses of dalbavancin with 750 mg on Day 1, a total of 10 subjects received 500 mg on Day 8 (7 out of 10 were found to have their creatinine clearance improved to ≥ 30 mL/min and 3 out 10 still had creatinine clearance < 30 mL/min). The remaining 5 subjects received 375 mg of dalbavancin on Day 8.

Thirty two subjects received only a single dose of dalbavancin; all but 1 of these 32 patients prematurely discontinued from study drug therapy. The remaining patient missed the second dose of dalbavancin in error. Twenty nine of these 32 patients received a single dose of dalbavancin 1000 mg and the remaining 3 subjects received a single dose of dalbavancin 750 mg due to underlying renal impairment.

Overall, the exposure to dalbavancin in the conducted clinical trials was appropriate in terms of doses and durations of treatment.

The comparator arms in the DUR001-301 and DUR001-302 trials included vancomycin only (n=100) or vancomycin and linezolid (n=551), **Table 38**. For the purpose of safety analyses vancomycin and vancomycin /linezolid treated subjects were pooled together.

Table 38: Comparator Drugs in Trials DUR001-301 and DUR001-302.				
	DUR001-301	DUR001-302	**Total**	
Vancomycin	66	34	**100**	**651**
Vancomycin/Linezolid	218	333	**551**	

7.2.2 Explorations for Dose Response

As indicated in 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations section, the vast majority of patients received the planned 2-dose regimen of dalbavancin so explorations for dose response have not been conducted in phase 3 clinical trials.

7.2.3 Special Animal and/or In Vitro Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

A total of 14 phase 1 clinical trials have been conducted to evaluate dalbavancin pharmacokinetics in healthy subjects and in subjects with renal and hepatic impairment. Since in vitro studies suggested that dalbavancin is not a substrate, inducer, or inhibitor of hepatic cytochrome P450 (CYP) isoenzymes, no clinical drug-drug interaction studies have been conducted. Drug-drug interactions were as evaluated by evaluating AE profiles in subjects in phase 2 and 3 trials who received concomitant medications of special interest. These medications included aztreonam, aminoglycosides, warfarin, and statins. However limited, the results of these analyses did not demonstrate any increase in AEs in dalbavancin-treated subjects who were receiving the medications of interest and did not indicate any specific drug interactions.

7.2.4 Routine Clinical Testing

In trials DUR001-301 and -302, baseline clinical assessments were performed within 24 hours before the first dose; efficacy and safety assessments were made on Days 2, 3, 4, 8, and 14 or 15 of the treatment period. An EOT assessment took place on Days 14 or 15, or within 3 days following premature discontinuation of treatment. The short-term follow-up visit (SFU) was to be targeted for Day 28, but could have occurred from Day 26 through Day 30. The long-term follow-up visit (LFU) was to be targeted for Day 70, but could have occurred from Day 60 through Day 88. Efficacy and safety assessments were also made at these visits. Hematology and chemistry laboratory evaluations were performed at Baseline, Day 3 and Days 14 or 15. The reader is referred to section 5.3 Discussion of Individual Studies/Clinical Trials for more details.

In DUR001-301 and -302 trials, only a baseline ECG was obtained. However, a separate thorough QT study was conducted by the Sponsor, see section 7.4.4 Electrocardiograms (ECGs), which identified no significant effects of dalbavancin on ECG parameters. Overall, routine clinical assessments in the dalbavancin development program were adequate.

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

As a glycopeptide, dalbavancin may be associated with infusion-related reactions, nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia.

The potential for ototoxicity was evaluated with audiometric testing in a total of 105 subjects in six phase 1 trials. Initially audiometric testing was undertaken in study VER001-1 where abnormal audiograms were recorded for 5 subjects treated with

dalbavancin and 2 treated with placebo. Subsequently, audiometric testing was performed in studies VER001-2, VER001-3, VER001-10, VER001-12, and VER001-13. The data were reviewed by a single central reviewer who concluded that there was no evidence of ototoxicity associated with dalbavancin. No audiometric testing was included in subsequent clinical trials.

As to other potential AEs associated with glycopeptides, routine clinical evaluations and laboratory testing conducted in the dalbavancin development program allowed their adequate assessment. The results of these analyses are presented in sections 7.4.1 Common Adverse Events and 7.4.2 Laboratory Findings.

7.3 Major Safety Results

7.3.1 Deaths

All the deaths in the dalbavancin development program occurred in phase 2 and 3 trials. No deaths occurred in Phase 1 trials. Overall, there were somewhat fewer deaths in the dalbavancin as compared to the comparator treated subjects, **Table 39**. No deaths were considered to be related to study drug.

Table 39: Deaths that Occurred During Dalbavancin Development Program

Prior Phase 2 and 3 Trials [a]		DUR001-301 and 302		All Phase 2 and 3 trials	
Dalbavancin (N=1126)	Comparator (N=573)	Dalbavancin (N=652)	Comparator (N=651)	Dalbavancin (N=1778)	Comparator (N=1224)
9 (0.8%)	7 (1.2%)	1 (0.15%)	8 (1.2%) [b]	10 (0.6%)	15 (1.2%)

[a] VER001-4, VER001- 5, VER001-8, VER001-9, and VER001-16
[b] Subject 959-277 from the vancomycin arm in trial 302 died after being withdrawn from the trial. The reason for withdrawal was an infection with Gram-negative pathogens.

A total of 16 deaths occurred in prior dalbavancin trials, 9 (0.8%) in the dalbavancin and 7 (1.3%) in comparator arm, **Table 40**.

Table 40: Number of Deaths in Prior Dalbavancin Trials

Trial	Phase	Number of subjects		Deaths	
		Dalbavancin	Comparator	Dalbavancin	Comparator
All trials		**1085**	**552**	**9 (0.8%)**	**7 (1.3%)**
VER001-4	2	40	34	3	2
VER001-8	3	367	186	3	3
VER001-9	3	571	283	2	2
VER001-16	3	107	49	1	0

The listing of deaths that occurred in prior trials is presented in **Table 41**.

Table 41: Deaths in Prior Dalbavancin trials				
Study Arm	Age, Sex	Day of Treatment	Cause of Death	Relationship to study drug [a]
Dalbavancin	75 F	22	Respiratory failure	Unrelated
Dalbavancin	55 M	21	Cardiopulmonary failure	Unrelated
Dalbavancin	68 F	17	Cardiorespiratory arrest	Unrelated
Dalbavancin	67 F	2	Cardiogenic shock and Gram-negative bacteremia	Unrelated
Dalbavancin	84 M	21	Cardiac arrest	Unrelated
Dalbavancin	82 M	23	Cardiopulmonary failure	Unrelated
Dalbavancin	59 F	4	Cardiac asystole	Unrelated
Dalbavancin	55 M	10	Myocardial infarction	Unlikely related
Dalbavancin	74 F	10	Worsening CHF	Unrelated
Vancomycin	65 F	9	Cerebrovascular accident	Unrelated
Vancomycin	64 F	12	Gastric cancer	Unrelated
Cefazolin	76 M	21	COPD exacerbation	Unlikely related
Cefazolin	72 F	55	Acute coronary syndrome	Unrelated
Cefazolin	67 F	12	Cardiac arrest	Unrelated
Linezolid	47 M	12	Cerebrovascular accident	Unrelated
Linezolid	82 F	48	Pulmonary edema	Unrelated
[a] Investigator assessment				

Most of the deaths in prior trials were related to cardiovascular diseases. The reader is referred to the safety review by Dr. Imosili for more details. In summary, Dr. Imosili concluded that patient deaths were balanced in the dalbavancin and comparator groups and that there was no direct evidence for a relationship between dalbavancin and mortality in these patients.

In the new DUR001-301 and -302 trials, there were 1 (0.15%) and 8 (1.2%) deaths in the dalbavancin and comparator arms, respectively. Subjects with fatal outcome in these trials are listed in **Table 42**. Two subjects in the vancomycin group died while receiving study drug. All deaths were considered unrelated to study drug. The case narratives follow the table.

Table 42: Deaths in DUR001-301 and -302 Trials

Trial	Subject	Age	Sex	Arm	Days on Study Drug	Study Day of Death	Cause of Death [a]	Clinical Response at 48-72 hours	Clinical response at EOT[b]
301	304-212	73	F	Vancomycin	10	32	Congestive cardiac failure	Yes	Yes
301	511-190	62	F	Vancomycin	15	49	Systemic lupus erythematosus	Yes	Yes
301	607-191	79	F	Vancomycin	3	4	Acute cardiac failure	No	No
301	607-497	69	F	Vancomycin	5	5	Pulmonary embolism	Yes	No
301	673-400	68	M	Vancomycin	14	52	Hypovolemia and cardiopulmonary failure	No [c]	Yes
302	778-127	57	M	Vancomycin	13	38	Sudden death	Yes	Yes
302	914-184	78	F	Vancomycin	7	41	Cardiopulmonary failure	Yes	Yes
302	914-342	78	F	Dalbavancin	11	32	Sepsis due to retroperitoneal abscess	Yes	Yes

[a] All deaths were considered unrelated to study drug by the investigator
[b] EOT – end of treatment
[c] Subject was a non-responder at 48-72 hours due to fever
[d] Subject was withdrawn from the trial due to wound and blood cultures growing *E. coli.*

Narratives of Deaths

Trial 301, Subject ID 304-212 (Comparator)

This 73-year-old female presented with cellulitis on the left hand and left lower arm. Past medical history included rheumatic fever, severe mitral valve insufficiency, atrial fibrillation, renal insufficiency, hypothyroidism, and non-Hodgkin lymphoma.

The patient was received vancomycin from Day 1 through Day 3 and linezolid from Day 2 through Day 10. The patient was an Early Clinical Responder and a success at EOT on Day 11. On Day 31 the patient was admitted with congestive heart failure and died on Day 32 from congestive heart failure confirmed by autopsy. Investigators considered the death unrelated to study drug.

Trial 301, Subject ID 511-190 (Comparator)

This 62-year-old female presented with cellulitis on the right lower leg. One of two baseline blood cultures and culture of an ABSSSI site needle aspirate grew methicillin-susceptible *Staphylococcus aureus* (MSSA).

Past medical history included of systemic lupus erythematosus (SLE), diabetes mellitus, and chronic renal insufficiency with baseline levels of serum creatinine of 4.9 mg/dL. Baseline medications included prednisolone 15 mg orally once daily.

The patient received vancomycin from Day 1 through Day 15 and was an Early Clinical Responder and a success at EOT. Blood cultures drawn on Day 8 were negative. However, blood cultures drawn on Day 14 grew MSSA from all 4 aerobic/anaerobic bottles. No evaluation to identify an ongoing source of MSSA bacteremia or metastatic infectious foci was done. Repeat blood cultures obtained on Day 22 were negative. Of note, norfloxacin was administered from Days 17 to 30 by oral route for “lupus nephritis”.

The patient had her last study visit at short-term follow-up on Day 29, where she was found to be afebrile and having minimal residual signs of infection at the ABSSSI site.

On Day 41 the patient was hospitalized due “deterioration of systemic lupus erythematosus.” On Day 48 the patient was discharged from the hospital and on Day 49 she died at home, reportedly while sleeping. The investigator considered SLE as the cause of death. The death was considered unrelated to study drug.

MO comments: The cause of a sudden death of this patient is not clear although the death seems to be unrelated to study drug. Importantly, the patient should have been declared clinical failure at EOT because of the recurrence of MSSA bacteremia. The

narrative does not describe how recurrent bacteremia was treated. The patient was given norfloxacin for "lupus nephritis." Since the MSSA isolate was susceptible to levofloxacin, as confirmed by the reviewer, norfloxacin could contribute to resolution of bacteremia.

Trial 301, Subject ID 607-191 (Comparator)

This 79-year-old female presented with cellulitis on the neck, right side of the face, and right side of the chest. Past medical history included ischemic heart disease, hypertension, premature ventricular contractions and chronic obstructive pulmonary disease.

The patient was started on vancomycin. On Day 3 the patient was afebrile and the area of the ABSSSI erythema had decreased to 13.0 cm^2. On Day 4 the patient developed acute heart failure, became hypotensive and died 15 minutes after the onset of symptoms. The Investigator considered the death unrelated to study drug.

Trial 301, Subject ID 607-497 (Comparator)

This 69-year-old female presented with a traumatic wound infection of the left lower leg. Relevant medical history included hypertension, ischemic heart disease, congestive heart failure, and atrial fibrillation.

The patient received vancomycin and was an Early Clinical Responder. On Day 5 the patient developed dyspnea, then lost consciousness and died. Autopsy revealed pulmonary embolism secondary to deep vein thrombosis of the left shin. Pulmonary embolism was considered unrelated to study drug by the investigator.

Trial 301, Subject ID 673-400 (Comparator)

This 68-year-old male presented with cellulitis on the lower right leg. The patient received vancomycin through Day 5 and linezolid on Day 6 through Day 14. From Day 1 to 5 the patient was also treated with heparin 5000 IU subcutaneously 3 times daily for prevention of thrombosis. The patient was an Early Clinical Non-Responder due to fever and was clinical success at EOT.

On Day 28 the patient experienced melena, hematemesis, was hospitalized with gastrointestinal bleeding and on Day 29 underwent a gastric resection. On Day 52 the patient developed acute heart and respiratory failure and died. Autopsy was not performed. The Investigator considered the death unrelated to study drug.

Trial 302, Subject ID 778-127 (Comparator)

The 57-year-old male presented with cellulitis on the lower right leg. Past medical history included diabetes mellitus, coronary heart disease, and chronic kidney disease.

The patient received vancomycin from Day 1 through Day 4 and linezolid from Day 5 through Day 13. The patient was an Early Clinical Responder and clinical success at EOT.

On Day 38 the patient suddenly died. No autopsy was performed. The investigator considered the event to be unrelated to study drug.

Trial 302, Subject ID 914-184 (Comparator)

This 78-year-old female presented with cellulitis on the left lower leg. Past medical history included hypertension, coronary artery disease, and cirrhosis of the liver. The patient received vancomycin from Day 1 through Day 4 and linezolid from Day 5 through Day 7. The patient was an Early Clinical Responder and clinical success at EOT.

On Day 38 the patient was hospitalized for "septicemia." Blood cultures grew Gram-negative unidentified bacteria in both aerobic and anaerobic samples. The patient was treated with ciprofloxacin and gentamicin for septicemia, which was considered to be secondary to a urinary tract infection and bacterial peritonitis. On Day 41 the patient died from cardiopulmonary failure. Autopsy was not performed. The investigator considered the death unrelated to study drug.

Trial 302, Subject ID 914-342 (Dalbavancin)

This 78-year-old female presented with cellulitis on the left lower leg. Past medical history included hypertension, coronary artery disease, and rheumatoid arthritis. The patient received dalbavancin on Day 1 and Day 8 and was an Early Clinical Responder and success at EOT.

On Day 26 the patient was admitted with hypotension and died on Day 32 from sepsis due to a retroperitoneal abscess in the retrocecal area with a fistula into the gluteal area; the diagnosis was confirmed by autopsy. The investigator considered the death unrelated to study drug.

Trial 302, Subject ID 959-277 (Comparator)

This was a 50-year-old male who underwent incision and drainage of right thigh phlegmon. The patient had a history of spinal cord injury, chronic osteomyelitis of the right ischial bone with fistula, and right thigh abscess which required drainage approximately one month prior to enrollment.

The patient received vancomycin from Day 1 to Day 4 and linezolid from Day 4 to Day 7 and was a clinical responder at 48-72 hours. However, baseline cultures of the ABSSSI and baseline blood cultures grew *Escherichia coli.* Multiple repeat blood cultures of

wound and blood obtained on Day 7 also grew *E. coli*. The patient was discontinued from the study on Day 7 due to wound and blood-stream infection with *E. coli*. Computed tomography of the pelvis and right thigh revealed progression of bone destruction and sequestration, involving the right hip joint, right femur and iliac bone. On Day 24 the patient died from "Gram-negative bacterial sepsis." The investigator considered the event to be unrelated to study drug.

MO comments: The death of this patient is not related to study drug. Of note, the patient should not have been enrolled in the trial because of baseline exclusion criteria of osteomyelitis. The reviewer agrees with the Sponsor and Investigator's assessment that the deaths in DUR001-301 and DUR001-302 trials were not related to study drug.

7.3.2 Nonfatal Serious Adverse Events

The number of subjects with nonfatal serious adverse events (SAE) was relatively small in both treatment groups, and was lower in the dalbavancin, 17 (2.6%), than in the vancomycin/linezolid, 29 (4.4%), treated subjects. Dalbavancin-treated subjects experienced a total of 19 and vancomycin-treated subjects a total of 35 SAEs. The most commonly represented SAEs were reported under the category of infections and infestations, 9 (1.4%) events in the dalbavancin arm and 10 (1.5%) in the vancomycin/linezolid arm. Of note, the category of nonfatal SAE overlaps with AEs described in section 7.3.4 Significant Adverse Events. **Table 43** presents nonfatal serious adverse events.

Table 43: Nonfatal Serious Adverse Events

Body System Organ Class (SOC) / SAE	**Dalbavancin N=652 n (%)**	**Comparator N=651 n (%)**
Total number of subjects with nonfatal SAE	17 (2.6)	26 (4)
Total Number of Events	19	32
Infections and Infestations [a]	9 (1.4)	9 (1.4)
Cellulitis	3 (0.5)	1(0.2)
Arthritis bacterial	2 (0.3)	0
Sepsis	1 (0.2)	1(0.2)
Bacterial sepsis	0	
Bacteremia	1 (0.2)	0
Embolic pneumonia	1 (0.2)	0
Necrotizing fasciitis	1 (0.2)	0
Gangrene	0	2 (0.3)
Abscess / Abscess limb	0	2 (0.3)
Diabetic foot infection	0	1 (0.2)
Rectal abscess	0	1 (0.2)
Appendicitis	0	1 (0.2)
Cardiac disorders	2 (0.3)	5 (0.8)

Table 43: Nonfatal Serious Adverse Events		
Body System Organ Class (SOC) / SAE	**Dalbavancin N=652 n (%)**	**Comparator N=651 n (%)**
Cardiac failure related events	1 (0.2)	5 (0.8)
Atrial fibrillation	1 (0.2)	0
Gastrointestinal Disorders	2 (0.3)	6 (0.9)
General Disorders and Administration Site Conditions	0	2 (0.3)
Sudden death	0	1 (0.2)
Systemic inflammatory response syndrome	0	1 (0.2)
Injury, poisoning and Procedural Complications	3 (0.5)	0
Metabolism and Nutritional Disorders	0	2 (0.3)
Systemic Lupus Erythematosus	0	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.2)	2 (0.3)
Pulmonary Embolism	1 (0.2)	1 (0.2)
Pulmonary Edema	0	1 (0.2)
Renal and urinary disorders	0	2 (0.3)
Nephropathy toxic	0	1(0.2)
Renal failure acute	0	1(0.2)
Immune system disorders	2 (0.3)	0
Anaphylactoid reaction	1 (0.2)	0
Food allergy	1 (0.2)	0
Erythema	0	1 (0.2)
Cholecystitis acute	0	1 (0.2)
Deep venous Thrombosis	0	1 (0.2)

A case of anaphylactoid reaction in the dalbavancin arm (subject DUR001-302-0927-0611), which was considered the only drug-related SAE reported is reviewed in further detail in section 7.3.4 Significant Adverse Events.

Medical Officer's comments: In addition to the case of anaphylactoid reaction, a case of drug rash with eosinophilia and systemic symptoms (DRESS) was reported in the dalbavancin arm (the case was not reported among the SAEs). Additional search for events related to hypersensitivity reactions was conducted. The results of the search are discussed in section 7.3.4 Significant Adverse Events.

7.3.3 Dropouts and/or Discontinuations

The rates of study drug discontinuation in trials DUR001-301 and DUR001-302 were similar in dalbavancin and comparator arms, 6.7% and 7.8%, respectively, **Table 44**. Adverse events were the main reasons for study drug discontinuation in the dalbavancin

and comparator arms, 11(1.7%) and 14 (2.1%), respectively. Overall, in all phase 2 and 3 trials, a total of 49/1778 (2.8%) subjects in the dalbavancin arm and 32/1224 (2.6%) subjects in the comparator arm discontinued study drug due to adverse events.

A total of 8 (1.2%) subjects in both arms discontinued study drug because of lack of efficacy.

Table 44: Study Drug Discontinuation in DUR001-301 and DUR001-302 trials

Reason for Discontinuation	Dalbavancin		Comparator	
	N	%	N	%
Randomized (ITT)	659	100.0	653	100.0
Received study drug	652	98.9	651	99.7
Study drug discontinued	44	6.7	51	7.8
Adverse event	11	1.7	14 [a]	2.1
Lack of efficacy	8	1.2	8	1.2
Withdrawal by subject	6	0.9	9	1.4
Subject non-compliance	3	0.5	0	0
Other	16	2.4	20	3.1

[a] One of 14 subjects received only placebo and 2 of 14 subjects died

Adverse events that resulted in discontinuation of study drug are presented in **Table 45**. No single category of these adverse events was prevalent in either study arm.

Table 45: Adverse Events Resulting in Discontinuation of Study Drug (Safety Population in Trials DUR001-301 and 302)

Dalbavancin (n=11)	**Comparator (n=13)[a]**
Hypersensitivity Reactions	
Drug eruption	Rash
Anaphylactoid reaction	Urticaria
	Hypersensitivity
	Swelling face and Pruritus
Infection-related events	
Cellulitis (n=2)	Erythema (worsening ABSSSI)
Osteomyelitis	Appendicitis
Arthritis bacterial	Rectal abscess
Necrotising fasciitis	
Bacteraemia and embolic pneumonia (baseline)	
Others	
Gastrointestinal haemorrhage	Renal failure acute
Alanine aminotransferase increased	Hyperglycemia
Procedural complication	Nausea
	Cardiac failure acute
	Arterial stenosis
	Pulmonary edema

[a] Subject who did not receive study drug is not included

Sixteen subjects in the dalbavancin and 20 subjects in the comparator arms discontinued the trials under the category of "Other." **Table 46** provides additional explanations for study drug discontinuations under this category. Overall, no imbalances in the reasons for study drug discontinuations were noted.

Table 46: Study Drug Discontinuation under the Category of "Other"; DUR001-301 and DUR001-302 trials

Safety population	Dalbavancin N=652	Comparator N=651
Discontinued as "Other"	16 (2.4%)	20 (3.1%)
Lost to follow-up	6	9
Infection with Gram-negative bacteria	3	3
Death	0	1
Other	7	7

MO comments: There are discrepancies between analyses datasets for adverse events (ADAE) and tabulation datasets for disposition (DS) and Phase 2/3 ADSL integrated dataset with regard to assigning adverse events as a reason for discontinuation of study drug.

As per ADAE datasets, there were 14 adverse events in the dalbavancin and 13 adverse events in the comparator arms that resulted in study drug discontinuations. These incidences are included in several tables in the Integrated Summary of Safety (ISS), e.g., Table 20.

Yet, as per disposition datasets and Phase 2/3 ADSL integrated dataset, a total of 11 in the dalbavancin and 14 subjects in the comparator arms discontinued study drug due to AEs. These incidences are indicated by the Sponsor in Table 12 in the ISS.

Analyses of the ADAE datasets for DUR001-301 and -302 trials identified 29 subjects who discontinued study drug due to adverse events. Analyses of disposition datasets demonstrated that 4 out of these 29 subjects, 3 in the dalbavancin and 1 in the comparator arm, discontinued study drug for other reasons. In the dalbavancin group one subject, DUR001-302-705-683, discontinued study drug because she was found to have an infection with Gram-negative bacteria and the other two subjects were discontinued due to lack of efficacy, subjects DUR001-302-763-270 and DUR001-302-960-067. A subject in the comparator arm, DUR001-301-102-123, was discontinued from study due to lack of efficacy rather than due to adverse events. In addition, one subject in the comparator arm, DUR001-302-786-165, received placebo, was discontinued due to AEs, but was not included in the safety population.

Therefore, the reviewer considers the incidences of discontinuations due to adverse events provided in Table 23 of this review, as well as by the Sponsor in Table 12 of the ISS, as more accurate.

7.3.4 Significant Adverse Events

Table 47 presents AEs in DUR001-301 and -302 trials that were categorized as severe. The number of subjects with severe AE were somewhat greater in the comparator than in the dalbavancin group, 26 (4%) and 18 (2.8%), respectively.

Table 47: Severe Adverse Events in DUR001-301 and -302 Trials

	Dalbavancin N=652			Comparator N=651		
SOC / Preferred term name	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**
Total	**22**	**17**	**2.6**	**33**	**24**	**3.7**
Infections and Infestations	**7**	**7**	**1.1**	**9**	**9**	**1.4**
Arthritis bacterial	2	2	0.3	0	0	0
Bacteraemia	1	1	0.2	0	0	0
Respiratory tract infection Viral	1	1	0.2	0	0	0
Cellulitis	1	1	0.2	0	0	0
Sepsis	1	1	0.2	1	1	0.2
Necrotising fasciitis	1	1	0.2	0	0	0
Localised infection	0	0	0	1	1	0.2
Rectal abscess	0	0	0	1	1	0.2
Bacteriuria	0	0	0	1	1	0.2
Abscess / Abscess limb	0	0	0	2	2	0.3
Appendicitis	0	0	0	1	1	0.2
Gangrene	0	0	0	2	2	0.3
Investigations	**1**	**1**	**0.2**	**0**	**0**	**0**
Blood glucose increased	1	1	0.2	0	0	0
Alanine aminotransferase increased				1	1	0.2
Blood and lymphatic system disorders	**3**	**3**	**0.5**	**1**	**1**	**0.2**
Anaemia	1	1	0.2	1	1	0.2
Neutropenia	1	1	0.2	0	0	0
Thrombocytosis	1	1	0.2	0	0	0
Gastrointestinal disorders	**2**	**1**	0.2	**7**	**4**	**0.6**
Gastric ulcer	1	1	0.2	0	0	0
Gastrointestinal bleed	1	1	0.2	0	0	0
Enterocutaneous fistula	0	0	0	1	1	0.2
Small intestinal obstruction	0	0	0	1	1	0.2
Nausea	0	0	0	1	1	0.2
Gastrointestinal haemorrhage	0	0	0	1	1	0.2

Table 47: Severe Adverse Events in DUR001-301 and -302 Trials						
	Dalbavancin N=652			Comparator N=651		
SOC / Preferred term name	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**
Abdominal pain	0	0	0	1	1	0.2
Peritonitis	0	0	0	1	1	0.2
Duodenal ulcer perforation	0	0	0	1	1	0.2
Renal and urinary disorders	**1**	**1**	**0.2**	**1**	**1**	**0.2**
Azotaemia	1	1	0.2	0	0	0
Renal failure acute	0	0	0	1	1	0.2
Respiratory, thoracic and mediastinal disorders	**2**	**2**	**0.3**	**1**	**1**	**0.2**
Epistaxis	1	1	0.2	0	0	0
Pulmonary embolism	1	1	0.2	1	1	0.2
General disorders and administration site conditions	**1**	**1**	0.2	**2**	**2**	**0.3**
Chills	1	1	0.2	0	0	0
Asthenia	0	0	0	1	1	0.2
Sudden death	0	0	0	1	1	0.2
Immune system disorders	**1**	**1**	0.2	**0**	**0**	**0**
Anaphylactoid reaction	1	1	0.2	0	0	0
Injury, poisoning and procedural complications	**1**	**1**	0.2	**1**	**1**	0.2
Procedural complication	1	1	0.2	0	0	0
Anaemia postoperative	0	0	0	1	1	0.2
Reproductive system and breast disorders	**1**	**1**	0.2	**0**	**0**	**0**
Uterovaginal prolapse	1	1	0.2	0	0	0
Skin and subcutaneous tissue disorders	**1**	**1**	0.2	**0**	**0**	**0**
Drug eruption	1	1	0.2	0	0	0
Vascular disorders	**1**	**1**	0.2	**1**	**1**	0.2
Hypertension	1	1	0.2	0	0	0
Deep vein thrombosis	0	0	0	1	1	0.2
Cardiac disorders	**0**	**0**	**0**	**4**	**4**	**0.6**
Cardiac failure congestive	0	0	0	1	1	0.2
Cardiac failure acute	0	0	0	1	1	0.2
Cardiopulmonary failure	0	0	0	2	2	0.3
Metabolism and nutrition disorders	**0**	**0**	**0**	**3**	**3**	**0.5**
Hypovolaemia	0	0	0	2	2	0.3
Type 1 diabetes mellitus	0	0	0	1	1	0.2

Table 47: Severe Adverse Events in DUR001-301 and -302 Trials						
	Dalbavancin N=652			**Comparator N=651**		
SOC / Preferred term name	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**2**	**2**	**0.3**
Osteoarthritis	0	0	0	1	1	0.2
Systemic lupus Erythematosus	0	0	0	1	1	0.2
Hepatobiliary disorders	**0**	**0**	**0**	**1**	**1**	**0.2**
Cholecystitis acute	0	0	0	1	1	0.2
One subjects may have more than one AE and may be counted several times, so the number of subjects in the rows does not match the total Generated from ISS Phase 2/3 ADAE Analysis Dataset, module 5.3.5.3						

Additional analyses of AEs related to hepatobiliary disorders, blood and lymphatic system disorders, hypersensitivity reactions, infusion site reactions, renal toxicity, and glucose metabolism were conducted. The analyses were prompted by potential clinical significance of these events, or their association with glycopeptides, dalbavancin's drug class, or safety signals identified during the safety review of the initial submission of NDA 21883.

Liver Function Tests Abnormalities

Several dalbavancin-treated subjects had significant elevations of liver function tests, more than observed in comparator treated subjects in trials DUR001-301 and -302. There were 6 subjects in the dalbavancin arm with alanine aminotransferase (ALT) elevation of greater than 5 times the upper limit of normal including 3 subjects with ALT > 10x ULN. No subjects in the comparator arm had this degree of ALT elevation. Liver function tests elevations in the DUR001-301 and -302 trials are presented in **Table 48**.

Table 48: Liver Functions Tests Elevations in DUR001-301 and DUR001-302 trials						
	Dalbavancin N = 652			Comparator N = 651		
	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
ALT ≥ ULN						
2x ULN	79	50	7.7	50	41	6.3
3x ULN	38	26	4	20	15	2.3
5x ULN	8	6	0.9	0	0	0
10x ULN	3	3	0.5	0	0	0
AST ≥ ULN						
2x ULN	66	44	6.7	38	28	4.3
3x ULN	27	21	3.2	14	12	1.8
5x ULN	9	8	1.2	4	4	0.6

Table 48: Liver Functions Tests Elevations in DUR001-301 and DUR001-302 trials

	Dalbavancin N = 652			Comparator N = 651		
ALP ≥ ULN						
2x ULN	24	12	1.8	23	15	2.3
3x ULN	3	2	0.3	12	6	0.9
5x ULN	0	0	0	2	1	0.2
TB ≥ ULN						
1.5x ULN	8	5	0.8	13	7	1.1
2x ULN	3	2	0.3	3	1	0.2
3x ULN	2	1	0.2	2	1	0.2

All measurements are post-baseline but subjects may have abnormal baseline levels. Subjects may be counted more than once in that they will be counted in all conditions (i.e., 2x, 3x, 5x) that apply.
ALP – alkaline phosphatase; TB – total bilirubin

Of note, the proportion of patients with elevated ALTs at baseline was similar in the two treatment arms, 13.9% in the dalbavancin and 14.5% in the vancomycin/linezolid arm. In addition, elevated baseline hepatobiliary status defined as the presence of either baseline ALT or AST of >3 times the ULN, or baseline alkaline phosphatase level of >1.5 times the ULN was found in 33 (5.1%) and 39 (6%) subjects in the dalbavancin and comparator arms, respectively.

Additional searches of the Medical History (MH) datasets for DUR001-301 and -302 trials were conducted by the reviewer in order to evaluate whether there was an imbalance between treatment arms in terms of baseline comorbidities that may have resulted in liver function tests elevation. A total of 172 such conditions, 74 in the dalbavancin and 98 in the comparator arm, were reported in 149 subjects, 66 (10.1%) in the dalbavancin and 83 (12.7%) in the comparator arm. The conditions were described with the following terms: hepatitis C (n=109), alcohol abuse (n=23), hepatic insufficiency (n=14), alcohol abuse (n=23), hepatitis B and chronic hepatitis B (n=9), fatty liver and severe fatty liver (n=5), cirrhosis, cirrhosis of the liver, hepatic cirrhosis and liver cirrhosis (n= 4), hepatitis A (n=2), elevated liver function and abnormal liver enzymes (n=2), diffuse changes of the liver and diffuse liver lesion, liver disease, and liver cysts multiple (n=4).

The distribution of selected conditions is presented in **Table 49**. Overall, there was no imbalance in baseline conditions potentially associated with liver disease that could explain a greater number of liver function test elevations in the dalbavancin arm.

Table 49: Selected Baseline Liver Diseases in DUR001-301 and DUR001-302 Trials						
	DUR001-301		DUR001-302		Total	
	Dalbavancin N=284 n (%)	Comparator N=284 n (%)	Dalbavancin N=368 n (%)	Comparator N=367 n (%)	Dalbavancin N=652 n (%)	Comparator N=651 n (%)
Events Total	37	55	37	43	74	98
Subjects Total	34 (12)	47 (16.5)	32 (8.7)	36 (9.8)	66 (10.1)	83 (12.7)
Hepatitis C	27 (9.5)	32 (11.3)	23 (6.3)	27 (7.4)	50 (7.7)	59 (9.1)
Alcohol abuse	4 (1.4)	12 (4.2)	4 (1.1)	3 (0.8)	8 (1.2)	15 (2.3)
Hepatic insufficiency	2 (0.7)	5 (1.8)	4 (1.1)	3 (0.8)	6 (0.9)	8 (1.2)
Hepatitis B	1 (0.4)	2 (0.7)	3 (0.8)	3 (0.8)	4 (0.6)	5 (0.8)
Not all comorbidities that may have resulted in liver function tests abnormalities are listed and a subject may have more than one problem						

Table 50 provides the number of subjects in dalbavancin clinical trials with normal baseline transaminases and post-baseline ALT elevation of greater than 3x ULN. Because ALT is a more specific marker of liver injury as compared to AST, only ALT was selected for elevations > 3 times of the ULN. Moreover, AST may be related to muscle damage especially in patients with soft tissue infection and surgeries, which is true of subjects in the dalbavancin trials. In trials DUR001-301 and -302, there were 6 such subjects with ALT elevation in the dalbavancin arm as compared to one subject in comparator arm. In all phase 2 and 3 clinical trials, there were 12 (0.8%) and 2 (0.2%) subjects in the dalbavancin and comparator arms, respectively, with normal baseline ALT and subsequent ALT elevations of greater than 3x ULN.

Table 50: Post- Dose Alanine Aminotransferase Elevations in Subjects with Normal Baseline Transaminase Levels in Dalbavancin Trials				
	DUR001-301&302		All Phase 2&3 Trials	
	Dalbavancin N=505	Comparator N=521	Dalbavancin N=1406	Comparator N=957
> 3x ULN – 5 ULN	3	1	7	1
> 5x ULN – 10x ULN	1	0	2	1
> 10x ULN	2	0	3	0
Total n (%)	6 (1.2)	1 (0.2)	12 (0.8%)	2 (0.2)
N - baseline ALT < the upper limit of normal; Subjects are counted once For trials DUR001-301 and 302 the measurements are obtained on Day 3 and End of Treatment visits (Day 14-15); for other trials (VER001-8 and VER001-9) measurements are obtained through the Test of Cure Visit (14 days following the completion of study medication)				

ALT transition profiles for the 6 subjects with post-baseline ALT elevation > 3x ULN in DUR001-301 and -302 trials are presented in **Table 51** and Figure 3. Follow-up

measurements obtained in 5 of 6 subjects demonstrated improvement or resolution of ALT elevations. All subjects received two doses of dalbavancin at 1000 mg on Day 1 and 500 mg on Day 8.

Table 51: ALT Transition Profiles in Subjects with Normal Baseline Transaminases and Post-dose ALT > 3x ULN in DUR001-301 and DUR001-302 Trials

Subject ID	Diagnosis	ALT levels (normal ranges 0-45 units/L)				
		Baseline	Day 3	EOT [a]	Day 20	Day 27-32
302-737-120	Abscess	29	28	589	127	-
302-927-428	Cellulitis	19	22	622	-	41
302-958-315	Cellulitis	33	274	17	-	-
302-747-505	Abscess	28	31	177	-	-
302-927-051	Cellulitis	34	26	175	-	13
302-944-360	Cellulitis	11	148	19	-	-

All subjects received 2 doses of dalbavancin
[a] EOT – End of Treatment, Day 14-16

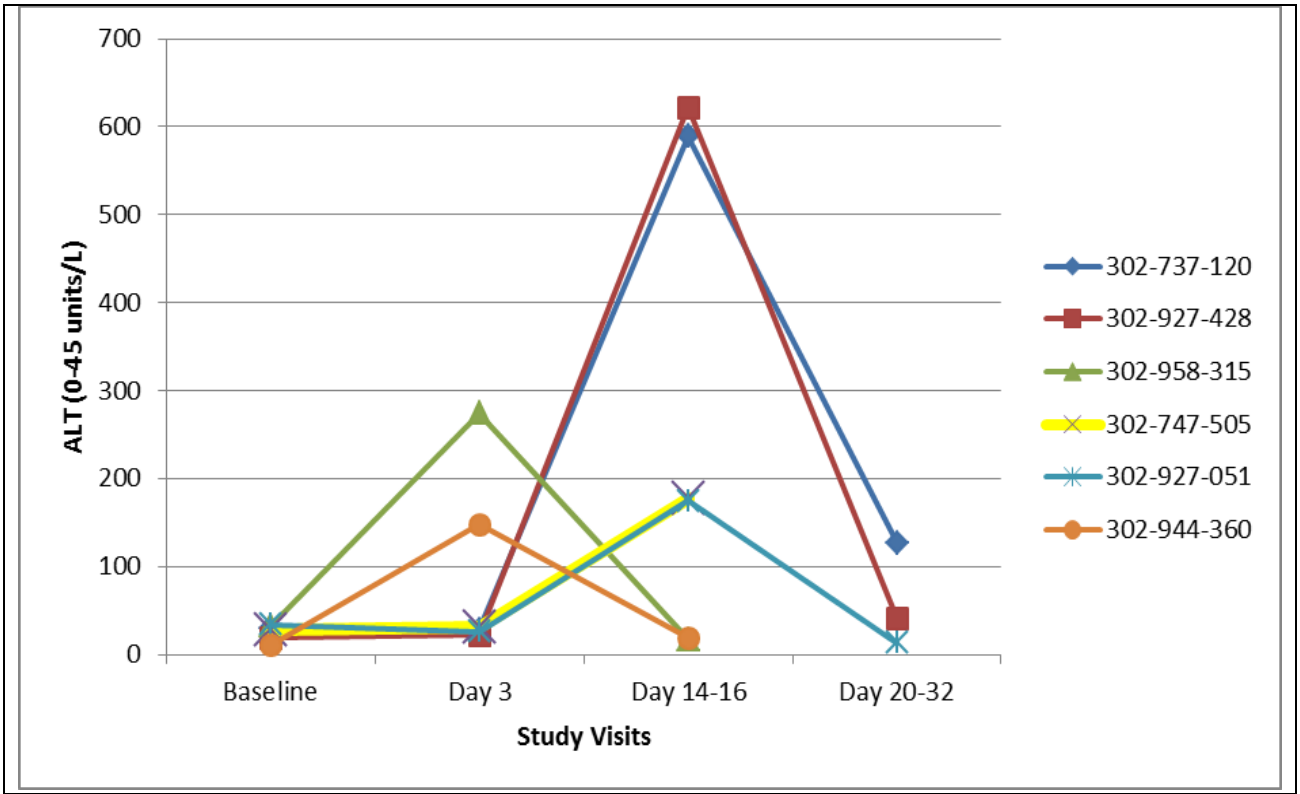

Figure 3: Timing of ALT Elevations in Dalbavancin-treated Subjects with Post-dose ALT > 3x ULN and Normal Baseline Transaminases

Associated elevation in other liver function test parameters and relevant medical history in these subjects is presented in **Table 52**. Concomitant medications for all subjects

except for subjects 747-505 and 927-051 are listed in **Table 53**. No concomitant medications were documented for subject 747-505 and subject 927-051 received only lidocaine for abscess incision.

Table 52: Concomitant Elevation in Liver Function Test Parameters in Subjects with Normal Baseline ALT and Post-baseline ALT Elevation > 3x ULN

Subject ID* Medical hist,	Highest ALT (0-45 units/L)	AST (0-41 units/L)	TB (0.1-1.2 mg/dL)	ALP	Baseline ALP (normal ranges)
927-428 Hepatitis C	622	85	5.8	210	121 (35-104 U/L)
737-120 Hepatitis C	589	248	0.6	274	135 (40-129 U/L)
958-315 Alcohol abuse	274	315	0.4	244	91 (40-129 U/L)
747-505 IV drug use	177	77	0.4	247	117 (40-129 U/L)
927-051 None	175	119	1.4	65	60 (35-104 U/L)
944-360 Chronic HBV	148	223	0.9	89	222 (35-104 U/L)

* All subjects are from trial 302 and had normal baseline ALT, AST and total bilirubin (TB) levels

One subject, 302-927-428, has concomitant total bilirubin elevation. This 47-year-old female with a history of hepatitis C received 1000 mg and 500 mg of dalbavancin on Day 1 and Day 8, respectively, for cellulitis. She also received ketorolac on study day 1 and 2 and metamizole on study day 1, both drugs are non-steroidal anti-inflammatory drugs. Her baseline ALT, AST, and total bilirubin levels were normal but ALP level was slightly elevated to 121 (normal range: 35 – 104 U/L). At EOT (day 14) her ALT was found to be > 10x ULN and total bilirubin elevation of > 4x ULN. ALP also rose to > 2xULN. ALT elevation resolved and bilirubin and ALP levels improved by Day 27. Shifts in liver function tests for this subject are presented in Figure 4 and in **Table 53**.

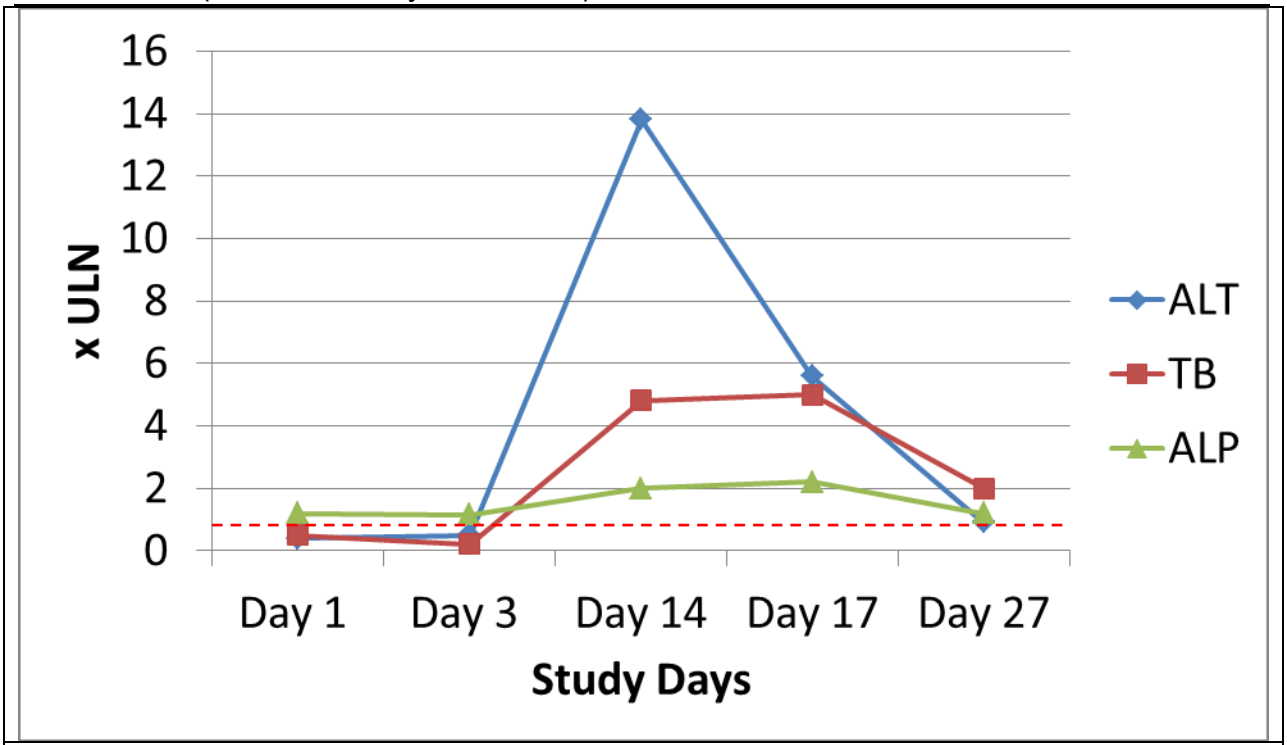

Figure 4: Liver function tests in subject 302-927-428.

Dashed red line indicates the upper limit of normal; TB – total bilirubin; ALP – alkaline phosphatase.

Medical Officer's comments: This subject has a noticeable concomitant elevation in ALT and total bilirubin. The case, however, does not meet Hy's Law criteria because of a history of hepatitis C and baseline elevation of alkaline phosphatase[4]. In addition, the subject received ketorolac which could have also caused ALT elevation. Ketorolac's label includes a precaution stating that the drug should be used with caution in patients with impaired hepatic function or a history of liver disease because treatment with ketorolac may cause elevations of liver enzymes and in patients with pre-existing liver dysfunction it may lead to the development of a more severe hepatic reaction. Nevertheless, elevations of liver function tests in this subject were associated with dalbavancin use.

The datasets for trials DUR001-301 and -302 were also searched for subjects with post-dose elevations in either ALT or AST elevations of ≥ 5x ULN and baseline transaminase levels < 2x ULN. There were 8 such subjects in the dalbavancin group and none in the comparator group, **Table 53**. Four out of 8 of had normal ALT at baseline and have been also included in **Table 52**. Post-baseline transaminase

[4] Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

elevations in these subjects are summarized in Figure 5. The transaminase (ALT or AST) with the highest elevation above the ULN is included.

Overall in trials DUR001-301 and -302, a total of 10 dalbavancin subjects had either ALT elevation > 3x ULN and normal baseline transaminases or transaminase elevation > 5x ULN with baseline transaminases < 2x ULN, **Table 52** and **Table 53**. Only one subject in the comparator group met these criteria. ALT rose concomitantly with AST in the majority of subjects and with ALP elevation in 4 subjects (ALP elevation was defined as ALP >2x ULN with no significant elevation at baseline). None of these 10 subjects with significant ALT elevations developed eosinophilia as a basis to suspect eosinophilic hepatitis, which may occur in response to some antibacterials.

Three out of 10 subjects had transaminase elevations at Day 3 and the other 7 subjects had transaminase elevations at EOT (day 14-16). All but one subject received two doses of dalbavancin (1000 mg on Day 1 and 500 mg on Day 8). One subject received only 1000 mg of dalbavancin on Day 1 and then study drug was discontinued due to insufficient therapeutic response.

Liver function tests abnormalities were documented to be resolved or significantly improved in 8 out of 10 subjects; 2 subjects did not have follow-up measurements. Of note, 2 out of 3 subjects with transaminase elevations at day 3 demonstrated resolution of liver function tests abnormalities at the EOT while continuing to receive dalbavancin. One of these 3 subjects with transaminase elevations at day 3 was also found to have almost complete resolution of transaminitis at EOT but this subject received only one dose of dalbavancin.

A total of 8 out of 10 subjects had a history of either of hepatitis C or chronic hepatitis B or alcohol abuse; in addition 1 subject has a history of current or recent IV drug use. Six of the 10 subjects received medications such as ketorolac, acetaminophen, carbepenems, betaxolol, and ropivacaine that could have contributed to liver function tests abnormalities.

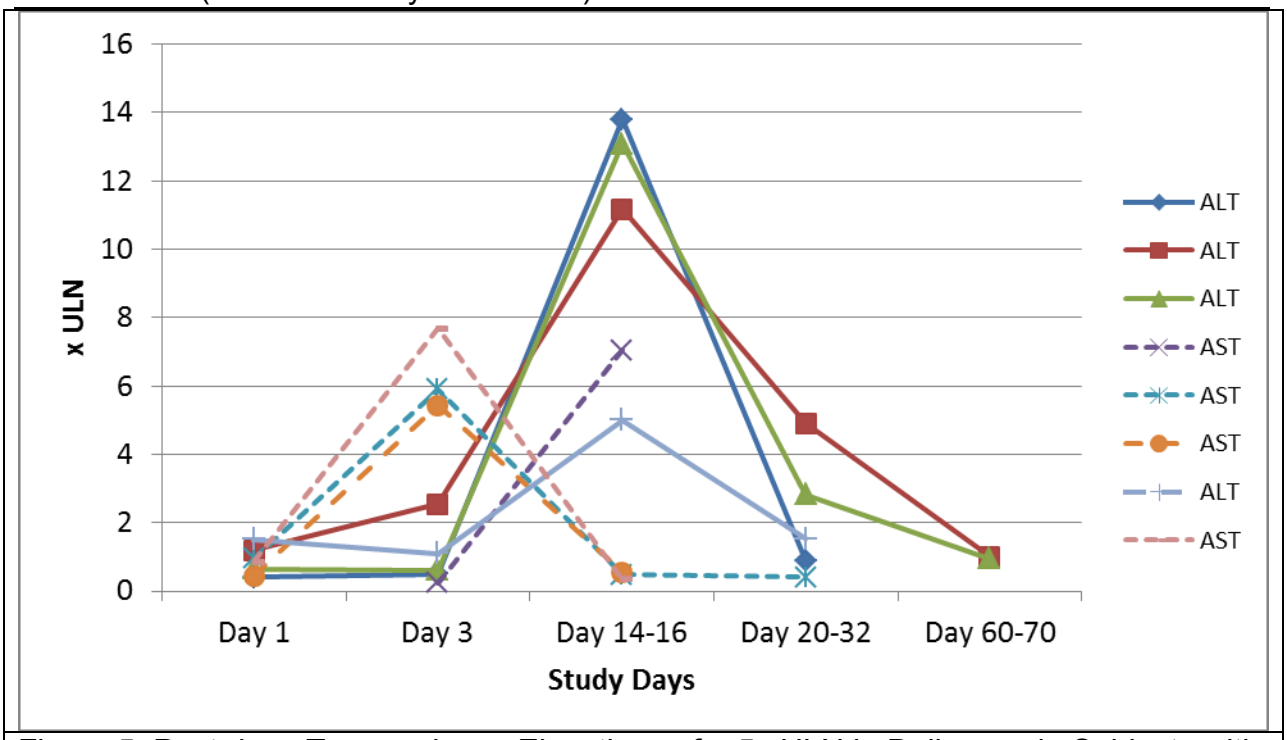

Figure 5: Post-dose Transaminase Elevations of > 5x ULN in Dalbavancin Subjects with Baseline Transaminase Levels of < 2x ULN

Table 53: Shifts in Liver Function Tests in Subjects with On Treatment Transaminase Elevations of Greater than 5 Times the Upper Limit of Normal in DUR001-301 and DUR001-302 Trials

Liver Function Tests [a]	Study Visits [b]										ABSSSI Type /Medical History	Concomitant. Medications
	Baseline Value	Day 3 Value	EOT		Interim visits		SFU		LFU			
			Study Day	Lab Value	Study Day	Lab Value	Study Day	Lab Value	Study Day	Lab Value		
ALT ≥ 10x ULN												
DUR001302-927-428												
ALT (0 - 45 U/L)	19	22	14	**622**	17	251	27	41	NA	NA	Cellulitis Hepatitis C	Metamizole Ketorolac
AST (0 - 41 U/L)	24	26	14	85	17	49	27	63	NA	NA		
TB (0.1-1.2 mg/dL)	0.6	0.2	14	**5.8**	17	**6.0**	27	2.4	NA	NA		
ALP (35 – 104 U/L)	121	120	14	**210**	17	**227**	27	126	NA	NA		
DUR001302-710-608												
ALT (0 - 45 U/L)	55	115	15	**503**	NA	NA	27	221	61	45	Cellulitis Alcohol abuse	Codeine Oxycodone Tramadol Diphenhydra-mine Lidocaine Promethazine
AST (0 - 41 U/L)	57	99	15	**200**	NA	NA	27	87	61	69		
TB (0.1-1.2 mg/dL)	0.2	0.3	15	0.2	NA	NA	27	0.5	61	0.4		
ALP (40-129 U/L)	91	94	15	139	NA	NA	27	146	61	111		
DUR001302-737-120												
ALT (0 - 45 U/L)	29	28	14	**589**	20	127	NA	NA	70	43	Abscess Hepatitis C Alcohol abuse	Ongoing heroin use
AST (0 - 41 U/L)	21	23	14	**248**	20	66	NA	NA	70	46		
TB (0.1-1.2 mg/dL)	0.5	0.3	14	0.6	20	0.3	NA	NA	70	0.3		
ALP (40-129 U/L)	135	106	14	**274**	20	182	NA	NA	70	113		
ALT or AST ≥ 5x ULN -10x ULN												
DUR001301-121-075												
ALT (0 - 45 U/L)	NA	55	15	**147**	NA	NA	NA	NA	NA	NA	Cellulitis Hepatitis C Alcohol abuse	None
AST (0 - 41 U/L)	NA	10	15	**289**	NA	NA	NA	NA	NA	NA		
TB (0.1-1.2 mg/dL)	NA	0.6	15	0.8	NA	NA	NA	NA	NA	NA		
ALP (40-129 U/L)	NA	91	15	122	NA	NA	NA	NA	NA	NA		
DUR001302-763-270												
ALT (0 - 45 U/L)	76	**202**	10	33	14	12	28	7	NA	NA	Cellulitis Alcohol abuse	Acetaminophen Aztreonam Imipenem Meropenem Ampicillin
AST (0 - 41 U/L)	39	**242**	10	60	14	20	28	17	NA	NA		
TB (0.1-1.2 mg/dL)	0.3	0.4	10	0.4	14	NA	28	NA	NA	NA		
ALP (35-104 U/L)	94	192	10	182	14	123	28	75	NA	NA		

Table 53: Shifts in Liver Function Tests in Subjects with On Treatment Transaminase Elevations of Greater than 5 Times the Upper Limit of Normal in DUR001-301 and DUR001-302 Trials

Liver Function Tests [a]	Study Visits [b]										ABSSSI Type /Medical History	Concomitant. Medications
	Baseline Value	Day 3 Value	EOT		Interim visits		SFU		LFU			
			Study Day	Lab Value	Study Day	Lab Value	Study Day	Lab Value	Study Day	Lab Value		Vancomycin Chlorpheniramine Ornithine
DUR001302-944-360												
ALT (0 - 45 U/L)	11	**148**	16	19	NA	NA	NA	NA	NA	NA	Cellulitis Chronic hepatitis B Alcohol abuse	Paracetamol Betaxolol Indapamide
AST (0 - 41 U/L)	18	**223**	16	23	NA	NA	NA	NA	NA	NA		
TB (0.1-1.2 mg/dL)	0.8	0.9	16	0.9	NA	NA	NA	NA	NA	NA		
ALP (35-104 U/L)	222	89	16	257	NA	NA	NA	NA	NA	NA		
DUR001302-958-055												
ALT (0 - 45 U/L)	68	49	14	**225**	20	69	NA	NA	NA	NA	Traumatic wound infection Alcohol abuse	Ketoralac Midozalam Ephedrine Bupivacaine Tetraspan
AST (0 - 41 U/L)	NA	25	14	71	20	31	NA	NA	NA	NA		
TB (0.1-1.2 mg/dL)	0.6	0.6	14	0.6	20	0.2	NA	NA	NA	NA		
ALP (40-129 U/L)	47	44	14	62	20	50	NA	NA	NA	NA		
DUR001302-958-315												
ALT (0 - 45 U/L)	33	**274**	14	17	NA	NA	NA	NA	97	45	Cellulitis Alcohol abuse	Ropivacaine Tetanus anatoxin
AST (0 - 41 U/L)	35	**315**	14	14	NA	NA	NA	NA	97	35		
TB (0.1-1.2 mg/dL)	0.5	0.4	14	0.1	NA	NA	NA	NA	97	0.1		
ALP (40-129 U/L)	91	**244**	14	74	NA	NA	NA	NA	97	58		

[a] Subjects with greater than 2 times the upper limit of normal baseline transaminases elevation are excluded;
[b] All subjects but DUR001302-763-270 received 1000 mg dalbavancin on Day 1 and 500 mg on Day 2; subject DUR001302-763-270 received only 1000 dalbavancin on Day 1
EOT – end of treatment; SFU – short-term follow-up, LFU – long-term follow-up, TB – total bilirubin; ALP – alkaline phosphatase

Table 54 presents shifts in ALT in subjects with elevated baseline ALT levels. No noticeable post-dose ALT rise was noticed in these subjects.

Table 54: Post-dose ALT Shifts in Subjects with Elevated ALT at Baseline						
	Baseline	Post-Dose Shifts				
ALT	N=98	< ULN	> ULN – < 3x ULN	>3x ULN - 5x ULN	>5x ULN - 10x ULN	>10x ULN
>ULN - < 3x ULN	88*	9	65	11	1	1
>3x ULN – 5xULN	8	1	2	5	0	0
>5x ULN- 10x ULN	1	0	0	1	0	0
>10x ULN- 20x ULN	1	0	0	0	1	0
* Post-dose levels are available for 87 out of 88 subjects Only the highest level is counted; subjects are counted once						

There were two more dalbavancin-treated subjects with significant post-baseline elevations of liver function tests in the dalbavancin development program. One subject in VER001-8 trial of uSSSI, subject ID VER001-8-206-017, experienced ALT elevation of greater than 20x ULN at the test of cure, Day 27. This 33-year-old white male received 1 dose of dalbavancin. Baseline and end-of-treatment liver function tests were within normal limits, Table 55.

Table 55: Liver Tests of Subject VER001-8-206-017 Who Experienced ALT elevation > 20x ULN				
Liver Tests (Normal Range)	**Baseline Value**	**EOT (Day 8)**	**TOC (Day 27)**	**Day 35**
ALT (0 - 47 U/L)	14	16	953	317
AST (0 - 37 U/L)	23	25	716	83
TB (0 -19 umol/L)	10	6	8	10
ALP (40-135 U/L)	81	100	131	99
EOT – end of treatment; TOC – test of cure; TB – total bilirubin; ALP – alkaline phosphatase				

On Day 27 the subject's ALT and ALT were 953 U/L and 716 U/L, respectively. ALP and total bilirubin levels remained normal. Follow-up conducted on Day 35 showed improving in transaminases levels. The investigator attributed the liver function abnormalities to alcoholic hepatitis rather than to study drug. The clinical reviewer, however, questioned this assessment and indicated that causal relationship of dalbavancin to transaminase elevations cannot be ruled out.

Another subject with post-dose ALT and AST elevation > 20x ULN and no significant changes in other liver function tests was enrolled as a healthy control in a phase 1 trial of safety and pharmacokinetics of dalbavancin in subjects with hepatic impairment, study VER001-12, subject ID 12001004. In this study, dalbavancin was administered at 1000 mg on Day 1 and 500 mg on Day 8.

This was a 43-year-old male with normal chemistry laboratory values from baseline through Day 22. On Day 60, the subject was found to have an alkaline phosphatase level of 168 IU/L (normal ranges 38-126), direct bilirubin of 0.7 mg/dL (normal ranges 0.1-0.5), AST of 1709 IU/L (normal ranges 15-41), ALT of 2525 IU/L (normal ranges 17-63), GGT 195 IU/L (normal ranges of 7-50), and LDH of 655 IU/L (normal ranges 98-192); indirect bilirubin was within normal ranges. Repeat liver function tests on unspecified dates remained elevated: AST of 149 IU/L and 184 IU/L, ALT of 210 IU/L and 332 IU/L, and GGT of 108 IU/L. Viral hepatitis tests were performed anti-HCV antibodies were reported positive whereas HBsAg and anti-hepatitis A IGM were negative. The subject was informed of his hepatitis C status. Subsequent clinical development is unknown.

Medical Officer's comments: Because viral hepatitis serologies weren't evaluated at baseline in this phase 1 study, it is uncertain whether this subject's liver function tests abnormalities were caused by an acute hepatitis C infection or resulted from exposure to dalbavancin in the setting of chronic hepatitis C.

Overall, the hepatic impairment trial enrolled 17 subjects with hepatic impairment and 10 healthy controls. There were 6 subjects with Child-Pugh Class A (mild hepatic impairment), 6 subjects with Child-Pugh Class B (moderate hepatic impairment), and 5 subjects with Child-Pugh Class C (severe hepatic impairment). Dalbavancin was administered in its therapeutic dose, i.e. 1000 mg on Day 1 and 500 mg dose on Day 8. Blood samples were collected over the 60 days of study participation. No difference in the frequency and severity of adverse events between study groups was found. The study concluded that no dosage adjustments are required in future clinical studies for patients with hepatic impairment.

Medical Officer's comments: although none of the dalbavancin-treated subjects with liver function tests elevation met Hy's law criteria, the degree of elevation and imbalance in liver function tests abnormalities between dalbavancin and comparator arms suggest the possibility of drug-induced liver injury (DILI) associated with dalbavancin.

The majority of dalbavancin-treated subjects with liver abnormalities that were discussed above developed a hepatocellular pattern of DILI, although 2 subject developed mixed injury, if categorized based on the R ratio as defined by modified

definitions of the Council for International Organizations of Medical Sciences[5]. The R ratio is a ratio of the ALT to the ALP relative to their upper limits of normal, i.e. R= (ALT/ULN) / (ALP/ULN). DILI is categorized as follows:

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

Importantly, almost all subjects with significant transaminase elevations had baseline conditions such as viral hepatitis or alcohol abuse that may have predisposed them to liver injury. It is conceivable that dalbavancin may cause elevations of liver enzymes especially in patients with pre-existing liver dysfunction. Therefore, AEs related to hepatotoxicity may need to be addressed in the labeling and warrant close monitoring in the post-marketing period provided that the drug is approved.

In considering other possible reasons for transaminase elevations, besides baseline comorbidities and concomitant medications, one may think about muscle injury related to deep soft tissue infection or occurring at surgery for abscess drainage. Since creatine kinase was not a part of chemistry panel in the dalbavancin studies, this possibility cannot be fully assessed. However, the majority of patients with transaminase elevation had cellulitis rather than abscess and deep soft tissue infections were excluded from these trials. Moreover, AST rather than ALT elevations would be expected in muscle injury. Finally, transaminase elevations would be expected to be equally distributed between treatment arms.

Adverse Events Related to Hemorrhages

The safety databases for trials DUR001-301 and DUR001-302 were explored by conducting standardized MedDRA queries (SMQ). One analysis identified a greater number of adverse events in the SMQ “Haemorrhages” in the dalbavancin arm. A total of 12 treatment emergent adverse events in 12 (1.8%) dalbavancin subjects as compared to 3 events in 3 (0.5%) comparator subjects were reported. In all phase 2 and phase 3 trials, there were 36 (2%) versus 19 (1.55%) subjects included in the narrow SMQ “Haemorrhages” in the dalbavancin and comparator arm, respectively.

In trials DUR001-301 and -302, this SMQ included the following preferred terms:

- Dalbavancin arm: haemorrhagic anaemia (2), haematuria (2), gastrointestinal haemorrhage, melaena, haematochezia, upper gastrointestinal haemorrhage, petechiae, vessel puncture site haematoma, epistaxis, and spontaneous haematoma.
- Comparator arm (3 events in 3 subjects): rectal haemorrhage, gastrointestinal haemorrhage, and epistaxis.

[5] Leise MD, Poterucha JJ, Talwalkar JA. Drug-Induced Liver Injury. Mayo Clin Proc. 2014 Jan;89(1):95-106.

Two out of 12 events of hemorrhages in DUR001-301 and 302 trials were considered severe, 2 moderate, and 8 mild. Severe events included gastrointestinal hemorrhage (subject DUR001301-145-290) that occurred in 70 year-old male on study day 8 and required RBC transfusion. Study drug was discontinued. Gastrointestinal hemorrhage resolved and the subject was found to have a gastric ulcer. Another severe event was epistaxis (subject DUR001301-507-202) that occurred in 58 year-old female on study day 5 and required external nasal tamponade, The events resolved and study drug was continued.

The distribution of adverse events identified by a narrow MedDRA SMQ Haemorrhages is presented in **Table 56**.

Table 56: Adverse Events identified by a narrow MedDRA SMQ Haemorrhages

Prior trials [a]		DUR001-301 and -302		All Phase 2 and 3 Trials	
Dalbavancin	Comp	Dalbavancin	Comp	Dalbavancin	Comp
N=1126	N=573	N=652	N=651	N=1778	N=1224
24 (2.1%)	15 (2.6%)	12 (1.8%)	3 (0.5%)	36 (2.6%)	19 (1.6%)

[a] VER001-4, -5, 8, -9, and 16
Subjects counted once regardless of the number of events

Timing of adverse events related to hemorrhages is presented in

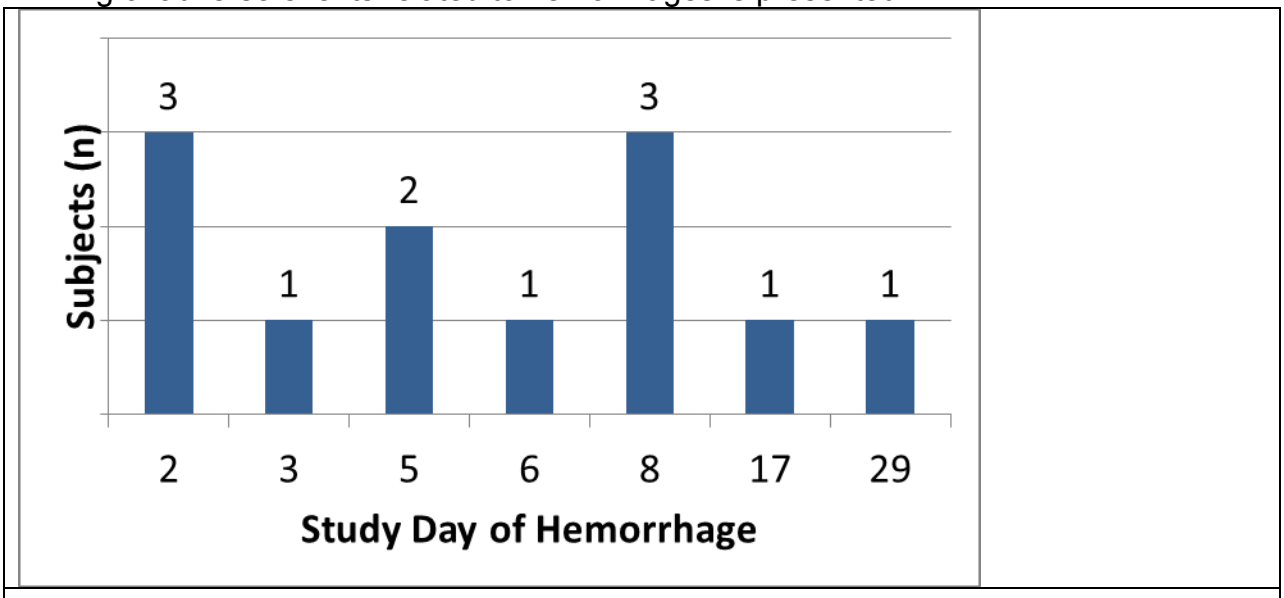

Figure 6: Timing of Treatment Emergent Adverse Events Related to Hemorrhages

Medical Officer's comments: There were more events related to hemorrhages in the dalbavancin arm. Of note, as described in section 4.3 Nonclinical Pharmacology/Toxicology, in an in vitro study dalbavancin inhibited collagen-induced platelet aggregation. Bleeding time or coagulation tests were not a part of the laboratory investigations in dalbavancin trials, so evaluation for associated coagulation

abnormalities was not feasible. No on-treatment decrease in platelet counts in subjects with adverse events identified by the SMQ Haemorrhages was observed in trials DUR001-301 and DUR001-302. Only 2 out of 12 subjects with hemorrhages received anticoagulants, namely enoxaparin.

Whether this difference in AEs related to hemorrhages is due to chance or indeed associated with dalbavancin is difficult to conclude at this point. Nevertheless, the observed imbalance in these events between dalbavancin and comparator warrants a closer attention to events of bleeding in the post-marketing period. It may be important, for instance for patients undergoing surgery or taking anticoagulants.

Hypersensitivity Reactions

An anaphylactoid reaction that was considered study drug related was reported in the dalbavancin arm in trial DUR001-302. This was a case of a 22-year-old white male with a past medical history of reactive airway disease that developed dyspnea, laryngospasm, and hypotension approximately 15 minutes after the start of IV infusion of dalbavancin 1000 mg on Day 1. The subject had also received general anesthetic agents approximately 3 hours prior and aztreonam intravenously immediately prior to the dalbavancin infusion. The dalbavancin infusion was stopped and epinephrine, hydrocortisone, midazolam, famotidine, chloropyramine (an antihistamine drug), and clemastine (an antihistamine and anticholinergic drug) were administered. Endotracheal intubation was not required and the symptoms and signs associated with the event completely resolved within approximately 1 hour of initiation of treatment with dalbavancin.

Another subject in the dalbavancin arm was diagnosed with eosinophilia and systemic symptoms (DRESS) syndrome; subject DUR001302-766-567. This was a 71-year-old male with cellulitis with baseline temperature of 38.8°C and baseline transaminase and eosinophil elevation, **Table 57**. The subject was declared a clinical responder at Day 3 and his temperature was 37.3°C at that time but an increase of eosinophil level up to $1.2x10^9$/L from a baseline level of $0.8x10^9$/L was noted. Study treatment was discontinued on Day 8 due to “allergic reaction” but the subject still received the second dose of dalbavancin. His temperature was 37.9°C on that day. On Day 10 the eosinophil count further increased to $8.6x10^9$/L and the temperature was 37.8°C. Transaminase levels did not increase. The subject was diagnosed with DRESS syndrome on Day 10. On Day 26 the syndrome was considered resolved.

Table 57: Laboratory and Temperature Data in a Subject with DRESS Syndrome

	Study Visits		
	Baseline	Day 3	Day 10
ALT (0-45 U/L)	117	68	94
AST (0-41 U/L)	45	31	47
Bilirubin (2-21 umol/L)	11	7	8

Eosinophils (0-0.7 10^9/L)	0.8	1.2	8.6
Eosinophils (0-7%)	8%	12	66
Temperature	38.8°C	37.3°C	37.9°C

Medical Officer's comments: the diagnosis of DRESS in this subject is not certain, although possible. DRESS is usually characterized by a longer latency, i.e. from 2 to 8 weeks from drug exposure whereas eosinophilia in this subject was noted at Day 3. Plus this subject did not have transaminase elevation which is a common component of DRESS.

The adverse event datasets for dalbavancin phase 2 and 3 clinical trials were searched for preferred terms related to hypersensitivity reactions. Overall, the number of subjects with preferred terms that may indicate allergic reactions was slightly higher in the comparator as compared to dalbavancin arm, 52 (8%) vs. 43 (6.6%) in the two new trials, and 140 (7.9%) vs. 115 (9.4%) in all phase 2 and 3 trials, respectively, **Table 58**.

Table 58: Adverse Events Related to Hypersensitivity Reactions

	DUR001-301 and 302 trials		**All phase 2 and 3 trials**	
	Dalbavancin N=652	**Comparator N=651**	**Dalbavancin N=1778**	**Comparator N=1224**
Total	**43 (6.6%)**	**52 (8%)**	**140 (7.9%)**	**115 (9.4%)**
Allergic oedema	1 (0.2%)	0	1 (<0.1%)	0
Anaphylactoid reaction	1 (0.2%)	0	1 (<0.1%)	0
Bronchospasm	0	1 (0.2%)	0	1 (<0.1%)
Dermatitis	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)
Dermatitis allergic	2 (0.3%)	3 (0.5%)	2 (0.1%)	3 (0.2%)
Drug eruption	1 (0.2%)	0	2 (0.1%)	0
Drug hypersensitivity	0	0	0	1 (<0.1%)
DRESS [a]	1 (0.2%)	0	1 (<0.1%)	0
Eosinophil percentage increased	0	0	1 (<0.1%)	0
Eosinophilia	2 (0.3%)	0	7 (0.4%)	5 (0.4%)
Eye irritation	2 (0.3%)	0	3 (0.17%)	0
Eye pruritis	0	0	1 (<0.1%)	0
Eye swelling	0	0	2 (0.1%)	0
Face oedema	0	0	0	1 (<0.1%)
Flushing	1 (0.2%)	4 (0.6%)	4 (0.2%)	8 (0.65%)
Food allergy	2 (0.3)	0	2 (0.1%)	0
Generalized erythema	0	0	0	1 (<0.1%)
Hot flush	0	0	1 (<0.1%)	2 (0.2%)
Hypersensitivity	3 (0.5%)	2 (0.3%)	5 (0.3%)	2 (0.2%)
Idiosyncratic drug reaction	0	0	0	1 (<0.1%)
Infusion site pruritus	0	0	4 (0.2%)	0

Table 58: Adverse Events Related to Hypersensitivity Reactions				
	DUR001-301 and 302 trials		All phase 2 and 3 trials	
	Dalbavancin N=652	Comparator N=651	Dalbavancin N=1778	Comparator N=1224
Total	**43 (6.6%)**	**52 (8%)**	**140 (7.9%)**	**115 (9.4%)**
Infusion site rash	1 (0.2%)	0	1 (<0.1%)	0
Infusion site urticaria	0	0	1 (<0.1%)	0
Injection site pruritis	1 (0.2%)	0	2 (0.1%)	0
Pruritus	6 (0.9%)	18 (2.8%)	32 (1.8%)	35 (2.9%)
Pruritus allergic	1 (0.2%)	0	1 (<0.1%)	1 (<0.1%)
Pruritus generalized	4 (0.6%)	5 (0.8%)	6 (0.3%)	9 (0.7%)
Rash	11 (1.7%)	9 (1.4%)	39 (2.2%)	22 (1.8%)
Rash generalized	1 (0.2%)	2 (0.3%)	2 (0.1%)	2 (0.2%)
Rash macular	0	1 (0.2%)	2 (0.1%)	2 (0.2%)
Rash maculo-papular	0	0	0	1 (<0.1%)
Rash papular	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)
Rash pruritic	1 (0.2%)	1 (0.2%)	4 (0.2%)	3 (0.2%)
Red man syndrome	0	0	0	2 (0.2%)
Swelling face	0	1 (0.2%)	2 (0.1%)	2 (0.2%)
Swollen tongue	0	0	1 (<0.1%)	0
Urticaria	0	3 (0.5%)	8 (0.4)	8 (0.7%)
[a] DRESS - Drug rash with eosinophilia and systemic symptoms				

Medical Officer's comments: Analyses of safety information provided in the submission do not demonstrate increased rates of hypersensitivity reactions in dalbavancin-treated subjects relative to comparators.

Of note, in DUR001-301 and -302 trials, no dalbavancin-treated subject developed red man syndrome as compared to 2 comparator-treated subjects. Yet, there was one subject in a thorough QT trial who developed red man syndrome while receiving an infusion of 1500 mg dalbavancin, see section 7.4.5 Special Safety Studies/Clinical Trials*.*

7.3.5 Submission Specific Primary Safety Concerns

The major safety finding is a possibility of dalbavancin-associated liver injury, especially in subjects with underlying liver disease. This finding is based on an observation of several cases of high-degree transaminase enzyme elevations in dalbavancin-treated subjects which was not observed in the comparator group.

Another safety finding is a higher rate of adverse events related to hemorrhages in dalbavancin-treated subjects, including gastrointestinal and soft-tissue hemorrhages. All events of hemorrhages were non-fatal and whether this imbalance is due to chance or indeed associated with dalbavancin is uncertain.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the incidence of TEAEs in DUR001-301 and -302 trials was similar in the dalbavancin and comparator arms. In the dalbavancin arm, a total of 214 (32.8%) subjects experienced 540 treatment emergent adverse events and in the vancomycin/linezolid arm a total of 247 (37.9%) subjects experienced 645 treatment emergent adverse events. The most common adverse events were nausea and headache. These events occurred at approximate rates of 4%-6% in both arms, **Table 59**.

Table 59: Treatment Emergent Adverse Events Observed in ≥1.5% of Subjects in Either Treatment Arm in Trials DUR001-301 and DUR001-302

MedDRA Preferred Term	Dalbavancin N=652	Comparator N=651
Nausea	27 (4.1)	28 (4.3)
Vomiting	11 (1.7)	10 (1.5)
Headache	25 (3.8)	23 (3.5)
Diarrhea	8 (1.2)	19 (2.9)
Hypertension	1 2 (1.8)	12 (1.8)
Constipation	12 (1.8)	11
Rash	10 (1.5)	9 (1.4)
Pruritus	6 (0.9)	18 (2.8)
Cellulitis	9 (1.4)	10 (1.5)
Oedema peripheral	7 (1.1)	11 (1.7)
Abscess limb	3 (0.5)	10 (1.5)

Table 60 presents all adverse events reported in DUR001-301 and -302 trials by System Oran Class (SOC). There were more adverse events in the dalbavancin-treated subjects reported under the SOCs of “Blood and lymphatic system disorders,” “Hepatobiliary disorders,” “Immune system disorders,” “Investigations,” “Nervous system disorders,” “Renal and urinary disorders,” and “Reproductive system and breast disorders.”

Events related to hepatobiliary disorders, blood and lymphatic system disorders, immune system disorders, investigations and renal disorders are discussed in section 7.3.4 Significant Adverse Events. Events related to nervous system disorders are discussed in this section. The events related to reproductive system disorders included erectile dysfunction, uterovaginal prolapse, prostatitis, and benign prostatic hyperplasia and were deemed not to be related to study drug and did not warrant further discussion.

Table 60: Adverse event analysis by Medical Dictionary for Regulatory Activities (MedDRA) in DUR001-301 and -302 trials

	Dalbavancin (N = 652)			*Comparator (N = 651)*			*Dalbavancin vs. Comparator*		
SOC	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*	*RD (per hundred)*	*RD C.I. (lower bound)*	*RD C.I. (upper bound)*
Blood and lymphatic system disorders	36	19	2.91	18	14	2.15	0.76	-0.94	2.47
Cardiac disorders	24	16	2.45	28	22	3.38	-0.93	-2.75	0.9
Congenital, familial and genetic disorders	1	1	0.15	0	0	0	0.15	-0.15	0.45
Endocrine disorders	0	0	0	1	1	0.15	-0.15	-0.45	0.15
Eye disorders	4	4	0.61	5	4	0.61	0	-0.85	0.85
Gastrointestinal disorders	99	63	9.66	124	73	11.21	-1.55	-4.87	1.77
General disorders and administration site conditions	61	50	7.67	78	52	7.99	-0.32	-3.24	2.6
Hepatobiliary disorders	7	7	1.07	5	4	0.61	0.46	-0.53	1.45
Immune system disorders	8	7	1.07	2	2	0.31	0.77	-0.13	1.66
Infections and infestations	63	46	7.06	112	78	11.98	-4.93	-8.1	-1.75
Injury, poisoning and procedural complications	11	10	1.53	11	10	1.54	0	-1.34	1.33
Investigations	85	50	7.67	59	37	5.68	1.99	-0.72	4.69
Metabolism and nutrition disorders	27	26	3.99	31	28	4.3	-0.31	-2.48	1.85
Musculoskeletal and connective tissue disorders	22	16	2.45	22	19	2.92	-0.46	-2.22	1.29
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2	2	0.31	0	0	0	0.31	-0.12	0.73
Nervous system disorders	48	42	6.44	47	35	5.38	1.07	-1.49	3.63
Psychiatric disorders	9	8	1.23	9	9	1.38	-0.16	-1.39	1.08

Table 60: Adverse event analysis by Medical Dictionary for Regulatory Activities (MedDRA) in DUR001-301 and -302 trials

	Dalbavancin (N = 652)			*Comparator (N = 651)*			*Dalbavancin vs. Comparator*		
SOC	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*	*RD (per hundred)*	*RD C.I. (lower bound)*	*RD C.I. (upper bound)*
Renal and urinary disorders	10	9	1.38	8	6	0.92	0.46	-0.7	1.62
Reproductive system and breast disorders	4	4	0.61	1	1	0.15	0.46	-0.21	1.13
Respiratory, thoracic and mediastinal disorders	19	16	2.45	23	21	3.23	-0.77	-2.58	1.03
Skin and subcutaneous tissue disorders	53	41	6.29	80	61	9.37	-3.08	-5.99	-0.17
Social circumstances	1	1	0.15	0	0	0	0.15	-0.15	0.45
Vascular disorders	23	21	3.22	34	28	4.3	-1.08	-3.15	0.99
Total	**617**	**459**	**70.4**	**698**	**505**	**77.6**			

Infusion Site Reactions

Because of the association of infusion site reactions with glycopeptides and the occurrence of infusion site reactions in preclinical dalbavancin studies this category of AEs was specifically reviewed.

In DUR001-301 and -302 trials, infusion site reactions occurred with similar frequencies in the dalbavancin and comparator arms. In two new trials, these reactions occurred in 12 (1.8%) dalbavancin and 14 (2.1%) comparator-treated subjects. In all phase 2 and 3 trials, there were somewhat fewer infusion site reactions in the dalbavancin arm relative to the comparator arm, 51 (2.9%) and 53 (4.3%), respectively. **Table 61** and **Table 62** list adverse events related to infusion site reactions that were observed in DUR001-301 and -302 and in the all phase 2 and 3 trials, respectively.

Table 61: Infusion site reactions in DUR001-301 and -302 Trials

	Dalbavancin (N=652)			Comparator (N=651)	
	Events	**Subjects n (%)**	**Day of AE***	**Events**	**Subjects n (%)**
Total (preferred terms)	**12**	**12 (1.8)**		**17**	**14 (2.1)**
Infusion site erythema	1	1 (0.2)	7	3	3 (0.5)
Infusion site extravasation	4	4 (0.6)	2;2;2;4	4	3 (0.5)
Infusion site irritation	1	1 (0.2)	2	0	0
Infusion site oedema	1	1 (0.2)	2	1	1 (0.2)
Infusion site pain	2	2 (0.3)	2;2	5	3 (0.5)
Infusion site phlebitis	0	0	NA	1	1 (0.2)
Infusion site rash	1	1 (0.2)	4	0	0
Infusion site reaction	0	0	NA	1	1 (0.2)
Infusion site swelling	1	1 (0.2)	2	1	1 (0.2)
Injection site cellulitis	0	0	NA	1	1 (0.2)
Injection site pruritus	1	1 (0.2)	1	0	0

* Day from the start of treatment; NA – not applicable

Table 62: Infusion site reactions in all Phase 2 and 3 Dalbavancin Trials						
	Dalbavancin (N=1778)			Comparator (N=1224)		
	Events	Subjects	%	Events	Subjects	%
Total (preferred terms)	51	51	2.9%	61	53	4.3%
Infusion related reaction	1	1	0.1	1	1	0.1
Infusion site coldness	2	2	0.1	0	0	0
Infusion site discomfort	1	1	0.1	0	0	0
Infusion site erythema	3	3	0.2	8	8	0.7
Infusion site extravasation	11	11	0.6	12	11	0.9
Infusion site haematoma	0	0	0	2	2	0.2
Infusion site inflammation	1	1	0.1	1	1	0.1
Infusion site irritation	1	1	0.1	4	2	0.2
Infusion site oedema	2	2	0.1	2	2	0.2
Infusion site pain	10	10	0.6	21	16	1.3
Infusion site phlebitis	1	1	0.1	1	1	0.1
Infusion site pruritus	4	4	0.2	0	0	0
Infusion site rash	1	1	0.1	0	0	0
Infusion site reaction	2	2	0.1	3	3	0.2
Infusion site swelling	3	3	0.2	4	4	0.3
Infusion site urticaria	1	1	0.1	0	0	0
Injection site cellulitis	0	0	0	1	1	0.1
Injection site discomfort	1	1	0.1	0	0	0
Injection site haematoma	1	1	0.1	0	0	0
Injection site irritation	1	1	0.1	0	0	0
Injection site pain	1	1	0.1	1	1	0.1
Injection site phlebitis	1	1	0.1	0	0	0
Injection site pruritus	2	2	0.1	0	0	0

Clostridium-difficile associated diarrhea (CDAD)

No subjects were diagnosed with Clostridium-difficile associated diarrhea in DUR001-301 and -302 trials. In the all phase 2/3 clinical trials dataset there were 4 (0.2%) subjects in the dalbavancin and 1 (0.1%) subject in the comparator arm that were diagnosed with CDAD.

Nervous system disorders

There were somewhat more subjects in the dalbavancin arm with adverse events related to the SOC of nervous system disorders, 42 (6.4%) versus 35 (5.4%),

respectively, Table 63. Analysis of the individual events demonstrates no meaningful difference between the dalbavancin and comparator arms with regard to adverse events.

Table 63: Subjects with AEs reported for the SOC "Nervous System Disorders" in DUR001-301 and 302 trials

	Dalbavancin N=652	Comparator N=651
Subjects	**42 (6.4)**	**35 (5.4)**
Averse Events [a]	**48**	**47**
Headache	27 (4.1)	28 (4.3)
Dizziness	10 (1.5)	7 (1.1)
Dysgeusia	3 (0.5)	0
Migraine	1 (0.2)	1 (0.2)
Sinus headache	1 (0.2)	5 (0.8)
Depressed level of consciousness	1 (0.2)	0
Hypertensive encephalopathy	1 (0.2)	0
Hypoaesthesia	1 (0.2)	1 (0.2)
Presyncope	1 (0.2)	0
Somnolence	1 (0.2)	0
VII th nerve paralysis	1 (0.2)	0
Loss of consciousness	0	1 (0.2)
Autonomic nervous system imbalance	0	1 (0.2)
Diabetic neuropathy	0	1 (0.2)
Diabetic encephalopathy	0	1 (0.2)
Paraesthesia	0	1 (0.2)

[a] One subject may have more than one event

Because no audiologic studies or specific evaluations for ototoxicity were conducted in the dalbavancin phase 2 and phase 3 clinical trials, the AEs suggesting ototoxicity were evaluated. The only adverse event found by the broad SMQs "Hearing and vestibular disorders" and "Vestibular disorders" was dizziness reported 8 (1.2%) dalbavancin and 6 (1%) comparator treated subjects (10 and 7 events, respectively). Otherwise, no AEs indicative of ototoxicity were reported.

7.4.2 Laboratory Findings

Liver function test abnormalities are discussed in section 7.3.4 Significant Adverse Events.

Hematological Abnormalities

Because hematopoietic abnormalities are known to be associated with glycopeptides, this group of adverse events was specifically explored. **Table 64** lists adverse events related to a decrease in white blood cell and platelet counts that were reported in DUR001-301 and -302 and all phase 2 and 3 trials.

Table 64: Adverse Events Related to Decrease in White Blood Cell and Platelet Count

	DUR001-301 and 302 trials		All phase 2 and 3 trials	
	Dalbavancin N=652	**Comparator N=651**	**Dalbavancin N=1778**	**Comparator N=1224**
Total *	**14 (2.1)**	**8 (1.2)**	**27 (1.5)**	**22 (1.8)**
Febrile neutropenia	0	0	2 (0.1)	0
Leukopenia	3 (0.5)	3 (0.5)	8 (0.4)	7 (0.6)
Lymphopenia	1 (0.2)	0	1 (<0.1)	0
Neutropenia	4 (0.6)	1 (0.2)	5 (0.3%)	1 (<0.1)
Neutropenic sepsis	0	0	0	1 (<0.1)
Pancytopenia	0	0	1 (<0.1)	1 (<0.1)
Platelet count decreased	0	1 (0.2)	2 (0.1)	1 (<0.1)
Thrombocytopenia	5 (0.8)	1 (0.2)	7 (0.4)	9 (0.7)
White blood cell count decreased	1 (0.2)	2 (0.3)	1 (<0.1)	2 (0.2)

* Preferred MedDRA terms reported in trials' datasets

The laboratory data datasets for phase 2 and 3 dalbavancin trials were also searched for post-dose decreases in white blood cell (WBC) and platelet counts in subjects with normal baseline blood cell counts. No significant differences were found in the rates of decreases in WBC and platelet counts between dalbavancin and comparator treated subjects, **Table 65**.

Table 65: Subjects with Post-Baseline Decrease in WBC and Platelet Counts				
	DUR001-301 and 302 trials		All phase 2 and 3 trials	
Subjects	Dalbavancin N=652	Comparator N=651	Dalbavancin N=1778	Comparator N=1224
WBC < LLN [a]	52 (8)	49 (7.5)	115 (6.5)	91 (7.4)
WBC ≤ 0.5x LLN [b]	1 (0.2)	0	2 (0.1)	6 (0.5)
WBC ≥ 0.75 decrease from baseline	5 (0.8)	7 (1.1)	12 (0.7)	10 (0.8)
Platelets < LLN [a]	36 (5.5)	41 (6.3)	60 (3.4)	74 (6)
Platelets ≤ 0.6 LLN [b]	7 (1.1)	4 (0.6)	9 (0.5)	8 (0.7)
Platelet ≥ 0.4 decrease from baseline	13 (2)	12 (1.8)	29 (1.6)	36 (2.9)

[a] Subjects with baseline blood cell count levels greater than the lower limit of normal (LLN) and any post-baseline blood cell count level less than LLN are included; subjects are counted once
[b] LLN – lower limit of normal, absolute values

Medical Officer's comments: no noticeable differences in decrease in white blood cell or platelet counts between dalbavancin and comparator arms were appreciated.

Renal Toxicity

Because renal toxicity is known to be associated with glycopeptides and the kidney was a target organ for toxicities in preclinical toxicology studies of dalbavancin, the adverse events related to renal impairment were explored, **Table 66**. The number of subjects with adverse events related to renal failure was overall low and the rates of renal impairment were similar in the dalbavancin and comparator arms.

Table 66: Adverse Events Related to Renal Toxicity				
	Dalbavancin N=652	Comparator N=651	Dalbavancin N=1778	Comparator N=1224
Total*	**1 (0.2)**	**4 (0.6)**	**7 (0.4)**	**12 (1)**
Renal failure	1 (0.2)	1 (0.2)	5 (0.3)	4 (0.3)
Renal failure acute	0	2 (0.3)	1 (0.1)	6 (0.5)
Renal failure chronic	0	1 (0.2)	0	1 (0.1)
Renal function test abnormal	0	0	1 (0.1)	0
Renal impairment	0	0	0	1 (0.1)

* Preferred terms reported in trial datasets for adverse events related to renal toxicity are included

Additional searches for post-baseline creatinine elevations were also conducted, **Table 67**. The table presents subjects with any post-baseline creatinine elevations, subjects with baseline creatinine below the upper limit of normal (ULN) and any post-baseline creatinine level greater than 1.5 times the ULN, and those with creatinine elevation greater or equal than 2 times the ULN regardless of a baseline level. In general, there were fewer subjects with post-baseline creatinine elevations in the dalbavancin arm.

Table 67: Subjects with Post-baseline Creatinine Elevation

	DUR001-301 and 302 trials		All phase 2 and 3 trials	
	Dalbavancin N=652	**Comparator N=651**	**Dalbavancin N=1778**	**Comparator N=1224**
Post-baseline Creatinine > ULN [a]	47 (7.2)	59 (9.1)	92 (5.2)	95 (7.8)
Creatinine ≥ 1.5x Upper Limit Absolute Value [a]	1 (0.2)	6 (0.9)	4 (0.2)	9 (0.7)
Creatinine ≥ 2 Fold Increase from Baseline [b]	1 (0.2)	7 (1.1)	9 (0.5)	12 (1)

[a] Subjects with baseline creatinine < the upper limit of normal and any post-baseline creatinine level > ULN
[b] Subjects with any level of baseline creatinine; subjects are counted once

Medical Officer's comments: safety data provided do not indicate that dalbavancin is associated with increased rates of renal toxicities relative to comparators.

Hyperglycemia and Hypoglycemia

The review of the initial submission of NDA 21883 found more subjects with hyper- and hypoglycemia in the dalbavancin arms. Thus, in trials VER001-8 and -9 a total of 6 (0.6%) and 5 (0.5%) out 938 dalbavancin-treated subjects developed hyper- and hypoglycemia, respectively as compared with 1 (0.3%) and 0 out 469 subjects with hyper- and hypoglycemia in the vancomycin arm. At that time concerns were raised about dalbavancin-associated glucose metabolism abnormalities.

The analysis of the incidence of hypoglycemia and hyperglycemia in the new trials as well as in all dalbavancin phase 2 and 3 trials does not demonstrate the increase in glucose metabolism abnormalities in the dalbavancin-treated patients. For the purpose of this analysis, hypoglycemia was defined as a glucose level less than 0.6 times the upper limit of normal at any post-baseline measurement. Hyperglycemia was defined as any elevation in glucose levels and as a glucose level greater than 3 times the upper limit of normal at any post-baseline measurement. The results of these analyses are presented in **Table 68**. In new trials hypoglycemia was observed in 1 (0.15%) dalbavancin-treated subject and in 4 (0.6%) vancomycin-treated subjects.

Table 68: Hypoglycemia and Hyperglycemia in Dalbavancin Trials						
	Prior trials [a]		DUR001-301 and -302		Total	
	Dalbavancin	Comp	Dalbavancin	Comp	Dalbavancin	Comp
	N=1126	N=573	N=652	N=651	N=1778	N=1224
Hypoglycemia	6 (0.5)	1 (0.2)	1 (0.2)	4 (0.6)	7 (0.4)	5 (0.4)
Hyperglycemia	58 (5.2)	31 (5.4)	14 (2.1)	14 (2.1)	72 (4)	45 (3.7)
[a] VER001-4, -5, 8, -9, and 16 Subjects counted once regardless of the number of events of hypo- or hyperglycemia.						

Lactate dehydrogenase

Lactate dehydrogenase (LDH) was a part of laboratory evaluations in the dalbavancin clinical trials. There were a greater number of post-dose LDH elevations among dalbavancin subjects relative to comparator groups, **Table 69**. Thus in DUR001-301 and -302 trial subjects with normal baseline LDH levels, a total of 10.7% of dalbavancin- and 7.3% of comparator-treated subjects had post-dose LDH increases.

The level of LDH ≥ 5 x ULN was pre-specified as a potentially clinically significant. There were 5 subjects with this level of post-dose LDH elevation, 2 in the dalbavancin and 3 in the comparator group; all these subjects had a normal baseline LDH levels.

Table 69: Post-dose LDH elevation in Subjects with Normal Baseline LDH Level			
DUR001-301 and -302 trials		All Phase 2 and 3 trials	
Dalbavancin n =534	Comparator n = 534	Dalbavancin n =1319	Comparator n = 933
57 (10.7)	39 (7.3)	188 (14.3)	108 (11.6)
LDH – lactate dehydrogenase; subjects with any post-dose level > ULN are included			

Hemoglobin

Because LDH elevations may potentially indicate hemolysis, hemoglobin levels were specifically evaluated. No significant differences in terms of hemoglobin levels were found. The number of subjects with a potentially clinically significant level of decrease in hemoglobin which was defined as a 0.25 fold decrease from the baseline were is presented in **Table 70**.

Table 70: Subjects with a 0.25 Fold Decrease in Hemoglobin from Baseline			
DUR001-301 and -302 trials		All Phase 2 and 3 trials	
Dalbavancin N=652	Comparator N=651	Dalbavancin N=1778	Comparator N=1224
6 (0.9%)	10 (1.5%)	22 (1.2%)	16 (1.3%)

7.4.3 Vital Signs

Vital sign measurements included pulse, respiration rate, systolic and diastolic blood pressure, and oral body temperature. The criteria used to identify potentially clinically significant (PCS) values and potentially clinically significant change (PCSC) in results are presented in Table 71.

Table 71: Criteria for Identifying PCS and PCSC Vital Sign Results

Parameter (units)	Normal Range	PCS Low Value	PCS High Value	PCSC Decrease in Value	PCSC Increase in Value
Pulse (bpm)	60-100	<50	>120	0.5x	2x
Respiration rate (bpm)	-	<8	>32	-	-
Systolic blood pressure (mmHg)	95-145	<85	>200	0.2x	1.6x
Diastolic blood pressure (mmHg)	60-95	<50	>120	0.2x	1.2x
Oral temperature (°Celsius)	-	-	-	2°	2°

PCS= potentially clinically significant; PCSC= potentially clinically significant change
Source: Integrated Summary of Safety, Table 92

No differences in changes in vital signs were identified in the dalbavancin and comparator arms, **Table 72**.

Table 72: Patients With Potentially Clinically Significant Changes in Vital Signs Results in Trials DUR001-301 and DUR001-302

	Dalbavancin N=652	Comparator N=651
Pulse (bpm)		
Increase ≥ 2x	0	0
Decrease ≥ 0.5	2 (0.3)	1 (0.2)
Systolic blood pressure (mmHg)		
Increase ≥ 1.6x	0	1 (0.2)
Decrease ≥ 0.2	3 (0.46)	1 (0.2)
Diastolic blood pressure (mmHg)		
Increase ≥ 1.2x	17 (2.6)	20 (3.1)
Decrease ≥ 0.2	11 (1.7)	11 (1.7)
Oral temperature (°Celsius)		
Increase ≥ 2° Celsius	0	0
Decrease ≥ 2° Celsius [a]		
Day 3	36.6% (218/595)	37.8% (220/582)
End of Treatment	41.4% (254/613)	40.9% (251/613)
Test of Cure	42.1% (233/554)	41.7% (227/544)

Measurements are obtained on Day 3, End of Treatment, and Test of Cure.
[a] The number of patients with available measurements at a specific time is used in computing percentages for this parameter. Source: Integrated Summary of Safety, Table 6-2.1.2

7.4.4 Electrocardiograms (ECGs)

A thorough QT clinical trial will be discussed in section 7.4.5, Special Safety Studies/Clinical Trials.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT Study

As per the applicant's analysis, a thorough QT study demonstrated that dalbavancin in IV doses up to 1500 mg did not prolong the QTc interval and had no effect on the heart rate, PR, or QRS interval.

This study DUR001-102 was a single-center, randomized, single-dose, placebo- and positive-controlled, partially double-blind, parallel-group ECG study to evaluate single IV doses of 1000 mg (therapeutic dose) and 1500 mg (supratherapeutic dose) dalbavancin.

The primary endpoint was a placebo-corrected, change-from-baseline QTcF across treatment groups. Two hundred healthy adult subjects (with at least 30% females) were randomized to 1 of the 4 treatment groups (50 subjects per treatment group):

- Group A (therapeutic dalbavancin dose): single IV dose of dalbavancin 1000 mg administered over 30 minutes
- Group B (supratherapeutic dalbavancin dose): single IV dose of dalbavancin 1500 mg administered over 30 minutes
- Group C (placebo dose): single IV dose of dalbavancin placebo (5% Dextrose for Injection administered over 30 minutes)
- Group D (moxifloxacin dose): single IV dose of dalbavancin placebo administered over 30 minutes and a single oral dose of moxifloxacin 400 mg tablet at the start of infusion.

Dalbavancin did not have an effect on the QTcF interval, and an effect exceeding 10 msec could be confidently excluded at all time points after a single dose of 1000 mg and 1500 mg. The largest placebo-corrected change-from-baseline QTcF after 1000 mg dalbavancin was 1.5 msec (CI: -0.6 to 3.6) at 6 hours and after 1500 mg was 0.2 msec (CI: -1.7 to 2.0) at 24 hours. There were no time points at which QTcF exceeded 480 msec or 500 msec in any of the treatment groups, and a change-from baseline QTcF exceeding 30 msec was observed in only 1 subject in the dalbavancin groups (1500 mg). Assay sensitivity was demonstrated by the expected effect of 400 mg moxifloxacin on QTcF, which peaked at 2 hours (mean 12.9 msec).

The most common AEs reported were infusion site reactions and nausea. Infusion site reactions were reported by 16 (32%) subjects in the dalbavancin 1500 mg group, 9 (18%) subjects in the dalbavancin 1000 mg placebo group, and 3 (6%) subjects in the

placebo group. Nausea was reported by 1 subject in each of the dalbavancin treatment groups and 3 subjects in the moxifloxacin treatment group.

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

There was one case of severe thrombocytopenia in the dalbavancin 1000 mg group. This was a 20-year-old female with a baseline platelet count of 167 x 10^3/μL (reference range 125-500 x 10^3/μL) who was found to have a platelet count of 19 x 10^3/μL on study Day 2. On Day 9 her platelet count was 100 x 10^3/μL. On Day 28 the platelet count was within the normal limits, 196 x 10^3/μL.

There was one case of ectopic pregnancy that was deemed not to be related to study drug.

There was one case of a mild AST elevation to 64 IU/L (reference range 5-46 IU/L) in a subject with normal baseline AST. Otherwise no significant changes in liver function tests were found in the dalbavancin groups.

Medical Officer's comments: No cases of red men syndrome in dalbavancin-treated patients were observed in phase 2 and 3 trials despite a relatively short 30-minute time of dalbavancin infusion. Of note, 1000 mg of dalbavancin were used in these trials. It is conceivable that when a higher dose of dalbavancin, i.e. 1500 mg, is administered over the same infusion time, the risk to develop red man syndrome is higher.

The event of profound thrombocytopenia in a healthy volunteer is probably related to dalbavancin since no other plausible cause is evident. Although the incidence of thrombocytopenia was overall similar in the dalbavancin and comparator arms in phase 2 and 3 trials, this adverse event warrants close monitoring in the post-marketing period.

7.4.6 Immunogenicity

Dalbavancin was evaluated for potential immunogenicity in guinea pigs in a standard intradermal sensitization study followed by dermal challenge. No guinea pigs had a positive response to the challenge.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The majority of subjects in phase 2 and 3 trials received a dalbavancin dose regimen of 1000 mg on Day 1 and 500 mg on Day 8 so explorations for dose dependency for AEs are limited. A total of 81 subjects received a dalbavancin dose that exceeded either the proposed total dose of 1500 mg or the proposed one time dose of 1000 mg. Safety assessments of these subjects are discussed in 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound. Overall, no evident increases in the incidence of AEs were observed in association with increased exposure to dalbavancin.

7.5.2 Time Dependency for Adverse Events

Since dalbavancin is intended for acute treatment, there are no data available to explore time dependence of adverse events with prolonged use. The duration of AEs was similar in the treatment arms. In all phase 2 and 3 trials the median duration of AEs was 3 vs. 4 days and in DUR001-301 and -302 trials the median duration of AEs was 4 vs. 3 days in the dalbavancin and vancomycin group respectively. The incidence of ongoing (not resolved during the study) AEs was similar in the dalbavancin and comparator groups in the phase 2 and 3 (14.2% vs. 15.7%) and DUR001-301 and -302 (6.1% vs. 9.1%) trials.

7.5.3 Drug-Demographic Interactions

The incidence of TEAE was similar between genders. In phase 2/3 trials 49.2% of dalbavancin-treated females and 51.7% of comparator-treated females had ≥1 TEAE. Among males, 42.1% of dalbavancin-treated subjects and 43.3% of comparator-treated subjects had ≥1 TEAE. Gastrointestinal (GI) disorders were the most common AEs for both genders. Among females, TEAEs related to in the GI disorders were experienced by 17.7% of dalbavancin-treated subjects and 19.1% of comparator-treated subjects. Among males, TEAEs in this SOC were experienced by 14% of dalbavancin-treated subjects and 14.6% of comparator-treated subjects.

The incidence of TEAE was also similar in subject ≥65 years and < 65 years of age. In the ≥65 years of age group, 50.5% of dalbavancin treated subjects and 47.2% of comparator-treated subjects had ≥1 TEAE. Among subjects <65 years of age, 43.8% of dalbavancin-treated subjects and 46.7% of comparator-treated subjects experienced ≥1 TEAE

There were somewhat more AEs reported among Black or African American patients in dalbavancin trials, **Table 73**. There was no imbalance, however, in the incidence of AEs

between the dalbavancin and comparator arms. GI disorders were the most common AEs for subjects in the dalbavancin and comparator groups who were White or Black or African American.

Table 73:Treatment Emergent Adverse Events by Race in Phase 2 and 3 Trials (Safety Population)		
Number of subjects with ≥1 TEAE, n/N1 (%)	Dalbavancin (N=1777)	Comparator (N=1223)
White	579/1388 (41.7)	448/1008 (44.4)
Black or African American	90/143 (62.9)	58/88 (65.9)
Asian	25/36 (69.4)	23/41 (56.1)
American Indian or Alaska Native	1/5 (20)	3/4 (75)
Native Hawaiian/Other Pacific Islander	1/1 (100)	0/1 (0)
Other	103/205 (50.2)	41/82 (50)
Source: Sponsor's Table 100 in the Integrated Summary of Safety		

With regard to geographic region, in phase 2/3 trials the highest rates of TEAEs were in subjects treated in the Asia-Pacific region, followed by North America, Eastern Europe/South Africa, and Western Europe with no imbalance between the dalbavancin and comparator arm, **Table 74**.

Table 74:Treatment Emergent Adverse Events by Geographic Region in Phase 2 and 3 Trials (Safety Population)		
Number of subjects with ≥1 TEAE, n/N1 (%)	Dalbavancin (N=1778)	Comparator (N=1224)
North America	636/1143 (55.6)	419/689 (60.8)
Eastern Europe/South Africa	104/395 (26.3)	112/389 (28.8)
Western Europe	42/216 (19.4)	26/118 (22)
Asia-Pacific	17/24 (70.8)	16/28 (57.1)
Source: Sponsor's Table 103 in the Integrated Summary of Safety		

7.5.4 Drug-Disease Interactions

In light of the imbalance in transaminase elevations observed in dalbavancin treated subjects, the association of transaminitis and baseline hepatobiliary status was of special interest. By the applicant's definition, baseline hepatobiliary status was considered elevated if either the subject's baseline ALT or AST was >3 times the ULN or if the subject's baseline alkaline phosphatase level was >1.5 times the ULN. Because many of the subjects with elevated hepatobiliary status had transaminase levels > 3 times the ULN at baseline, higher post-dose elevations, i.e. > 10 times the ULN were considered more relevant for the purpose of this analysis.

The number of subjects with elevated hepatobiliary status was small. In all phase 3 trials there were 76 and 76 subjects with elevated baseline hepatobiliary status in the dalbavancin and comparator arms, respectively. In DUR001-301 and -302 trials there were 33 and 39 subjects with elevated baseline hepatobiliary status in the dalbavancin and comparator arms, respectively.

Post-dose ALT elevations by baseline hepatobiliary status are presented in Table 75. Overall, no obvious association between hepatobiliary status as defined by the applicant and post-dose transaminase elevations was noted. The highest ALT elevations were observed in subjects with not elevated hepatobiliary status. It has to be re-emphasized that these inferences are limited due to small numbers of subjects with elevated hepatobiliary status.

Table 75: Post-Dose Alanine Aminotransferase Elevations by Hepatobiliary Status at Baseline

		>5x ULN – 10xULN	**> 10x ULN-20x ULN**	**> 20 x ULN**
	N	**n (%)**	**n (%)**	**n (%)**
Hepatobiliary Status Elevated				
All Phase 2 and 3 trials				
Dalbavancin	76	2 (2.6)	0	0
Comparator	76	7 (9.2)	1 (1.3)	0
DUR001-301 and -302				
Dalbavancin	33	2 (6.1)	0	0
Comparator	39	1 (2.6)	0	0
Hepatobiliary Status Not Elevated				
All Phase 2 and 3 trials				
Dalbavancin	1580	7 (0.4)	3 (0.2)	1 (0.1)
Comparator	1070	2 (0.2)	1 (0.1)	0
DUR001-301 and -302				
Dalbavancin	574	3 (0.5)	3 (0.5)	0
Comparator	577	0	0	0

Subjects with any baseline ALT levels are included

In addition, the incidence of AEs by creatinine clearance was evaluated. No imbalance between treatment arms in the incidence of AEs in subjects with or without renal impairment was noticed, **Table 76**.

Table 76:Treatment Emergent Adverse Events by Creatinine Clearance in Phase 2 and 3 Trials (Safety Population)		
	Number of subjects with ≥1 TEAE, n/N1 (%)	
Baseline Creatinine Clearance	Dalbavancin (N=1777)	Comparator (N=1223)
< 30 mL/min	15/32 (46.9)	9/21 (42.9)
30 to 59 mL/min	152/310 (49)	117/225 (52)
60 to 89 mL/min	226/504 (44.8)	162/344 (47.1)
≥ 90 mL/min	381/890 (42.8)	272/607 (44.8)
Source: Sponsor's Table 101 in the Integrated Summary of Safety		

7.5.5 Drug-Drug Interactions

No clinical drug-drug interaction studies have been conducted with dalbavancin. In vitro studies using human microsomal enzymes and hepatocytes indicate that dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes so drug-drug interactions between dalbavancin and drugs metabolized by cytochrome P450 are not anticipated.

In clinical trials, the potential for drug-drug interactions was evaluated by examining the proportions of subjects in the phase 2 and 3 trials who had AEs and received concomitant medications of special interest. The concomitant medications of special interest included aztreonam, aminoglycosides, warfarin, and statins. AEs that began on or after the start date of the concomitant medication were considered to have occurred during treatment with the specified concomitant medication. No specific drug-drug interactions have been observed in dalbavancin-treated subjects.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Long-term carcinogenicity studies were not conducted with dalbavancin because the drug showed no selective reproductive or developmental toxicity and was non-genotoxic. In addition, the proposed dosage regimen is limited to two weeks.

7.6.2 Human Reproduction and Pregnancy Data

Because pregnant subjects were excluded from dalbavancin studies, there are no data on human pregnancies exposed to dalbavancin. There were also no studies to determine the presence of dalbavancin in human milk.

There was one subject in the dalbavancin group with positive serum pregnancy test in trial VER001-9 and one subject with ectopic pregnancy (dalbavancin 1000 mg treatment group) in Study DUR001-10:

- Subject VER001-9-025-066, randomized to dalbavancin, had a negative urine pregnancy test at baseline and was menstruating at screening. The subject's serum pregnancy test result was found to be positive during infusion of the first dose of study medication. Study medication was immediately discontinued. The subject received only 7.2 mL of the infusion. A repeat serum pregnancy test on Day 10 was negative and the subject was still menstruating. No additional information was provided.

- Subject DUR001-0102-0180, a 39-year-old white female received 1000 mg of dalbavancin. The subject had an intrauterine device at the time of the study entry. Six days after infusion her serum beta human chorionic gonadotropin (ßhCG) was elevated (15.98 mIU/mL). Repeat tests drawn the next day and in 3 days after confirmed ßhCG elevations and were 21.72 mIU/mL and 36.55 mIU/mL, respectively. A transvaginal pelvic ultrasound conducted 11 days after dalbavancin administration confirmed an ectopic pregnancy in the right fallopian tube. The subject was administered methotrexate at that day to terminate the pregnancy. The termination of pregnancy was subsequently confirmed by normalized ßhCG levels.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and efficacy in pediatric patients have not been established. The only clinical trial in children that was competed at the time of this submission is a single dose PK trial in 10 pediatric subjects aged from 12 to 16 years that were hospitalized for a known or suspected bacterial infection. A dose of 1000 mg of dalbavancin was administered to subjects weighing 60 kg or greater (n=5) and a dose of 15 mg/kg was administered to subjects weighing < 60 kg (n=5) in addition to background anti-infective treatment.

Five subjects in the dalbavancin 1000 mg group and 4 subjects in the 15 mg/kg group experienced AEs. There were no severe AEs. There were no study discontinuations or dose reductions of treatment due to AEs. Headache, experienced by 1 subject in each group, was the only AE to be experienced by more than 1 subject. AEs experienced in the 1000 mg group were diarrhea, nausea, vomiting, increased blood bilirubin, headache, nasal congestion and hypotension. AEs experienced in the 15 mg/kg group were abdominal pain, constipation, ileus, hyperbilirubinemia, skin laceration, wound, dehydration, dizziness, headache and rash macular. No transaminase elevations were observed. No decreases in peripheral blood cell counts were observed either.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Eighty-one subjects received a dalbavancin dose that exceeded either the proposed total dose of 1500 mg or the proposed one time dose of 1000 mg, **Table 77**.

Table 77: Subjects Who Received a Dalbavancin does of Greater Than 1500 mg

Study	Phase	Population	Dalbavancin dose	No of Subjects N=81
DUR001-104	1	Healthy volunteers	2500mg – 4500 mg in multiple weekly doses	18
VER001-2	1	Healthy volunteers	1600 mg given in multiple doses	3
DUR001-101 (n=8) DUR001-102 (n=50)*	1	Healthy volunteers	1500 mg as a single dose	58
VER001-8	3	uSSSI	3000 mg as three doses of 1000 mg	1
DUR001-302	3	ABSSSI	3500 mg; 3000 mg on Day 1 and 500 mg on Day 8	1

* A thorough QT study
Abbreviations: ABSSI – acute bacterial skin and skin structure infection; uSSSI – uncomplicated skin and soft tissues infection

Doses of dalbavancin that exceed that proposed for the treatment of ABSSSI were investigated in study DUR001-104. This was an open-label safety, tolerability, and PK study of multiple weekly doses in 18 healthy volunteers between the ages of 18 and 55 divided in 3 cohorts. All subjects received 1000 mg dalbavancin at Day 1 and weekly doses of 500 mg of dalbavancin for up to 3, 5, or 7 additional weeks (up 4500 mg total exposure), **Table 78**.

Table 78: Extent of Exposure in DUR001-104 Trial

Cohort (Subject N)	Dalbavancin Doses Taken	Approximate Exposure to Therapeutic Dalbavancin Levels (weeks)	Total Exposure (mg)
Cohort I (N=6)	4 doses total – 1000 mg x 1 then 500 mg x 3	5	2500 mg
Cohort II (N=6)	6 doses total – 1000 mg x 1 then 500 mg x 5	7	3500 mg
Cohort III (N=6)	8 doses total – 1000 mg x 1 then 500 mg x 7	9	4500 mg

Seven subjects reported a total of 10 treatment emergent adverse events (TEAE) over the course of the study. Adverse events were mild to moderate in intensity. No serious adverse events were reported. No subjects were discontinued or withdrew due to an AE. The only TEAE reported by more than one subject was pain in extremity which was reported on 1 occasion by 2 subjects (11.1%), including 1 subject from Cohort I and 1 subject from Cohort III. Urticaria was reported beginning on Day 33 and ended on Day 38 on 1 occasion by 1 subject (16.7%) in Cohort 1 and was considered by the investigator to be moderate in intensity.

Review of hematology and biochemistry tests found no significant abnormalities. There was a mild increase in eosinophils percentage and absolute counts during study drug administration in three subjects. One subject had an elevation in alanine aminotransferase to 77 µmol/L (normal ranges 5-46) on day 14, without concomitant elevation in bilirubin or alkaline phosphatase, which resolved by day 21.

Fifty eight healthy subjects received a single dose of 1500 mg of dalbavancin in trials DUR001-102 (n=50), a thorough QT study, and DUR001-101 (n=8). Adverse events in trial DUR001-102 are described in section 7.4.5 Special Safety Studies/Clinical Trials. Noteworthy is a case of red man syndrome observed in the dalbavancin 1500 mg group.

DUR001-101 was a PK trial of a single dose of dalbavancin 1500 mg in healthy volunteers. In this trial four subjects experienced a total of 9 AEs over the course of the study. All AEs were mild (dysgeusia, nausea, diarrhea, muscle tightness, infusion site pain, chills and headache) or moderate (vomiting and pain) in intensity, and all resolved by Day 2. Clinical laboratory evaluations demonstrated an elevation of ALT and AST in one subject up to 106 IU/L (reference range 5-39) and 80 IU/L (reference range 5-46), respectively. The ALT and AST abnormalities subsequently resolved. One subject with an elevated baseline peripheral eosinophil count of $0.7x10^3$/µL (reference range 0-0.4) experienced an increase in eosinophil count up to $1.2x10^3$/µL after study drug dosing. No other significant laboratory abnormalities were noted.

Two subjects received a higher dose of dalbavancin in phase 3 trials because of medication errors:

- A 63-year-old male, subject VER001-8-022-001, who was enrolled in trial VER001-8 for uSSSI, received 3000 mg of dalbavancin that were administered as three 1000 mg doses in five days. There were no changes in the patient's liver or renal function tests and no signs of toxicity.

- A 36-year-old male, subject DUR001302-944-039, received a total dose of 3500 mg of dalbavancin that was administered as a 3000 mg dose on Day 1 and 500 mg dose on Day 8. The subject has a history of hepatitis B and C and a history of

intravenous drug abuse. No changes in the patient's liver or renal function tests were detected.

Overall, no evident increases in the incidence of AEs were observed in association with increased exposure to dalbavancin.

7.7 Additional Submissions / Safety Issues

No safety issues in addition to those described in this review have been identified.

8 Postmarket Experience

None.

9 Appendices

9.1 Literature Review/References

The references are included as footnotes.

9.2 Labeling Recommendations

A warning on the possibility of drug induced liver injury associated with dalbavancin use is being considered for inclusion in the dalbavancin label. The language of the warning as well as other labeling recommendations has not been yet formulated at the time of completion of this review.

9.3 Advisory Committee Meeting

An advisory committee meeting is scheduled on March 31, 2014, i.e. in approximately one month after the completion of this review.

9.4 Clinical Investigator Financial Disclosure

Application Number: 21883

Submission Date: 09/26/2013

Applicant: Durata Therapeutics International B.V.

Product: Dalbavancin hydrochloride

Reviewer: Dmitri Iarikov, MD, PhD, Division of Anti-Infective Products

Date of Review: 03/03/2014

Covered Clinical Study (Name and/or Number): A8841004, DUR001-101, DUR001-102, DUR001-103, DUR001-104, DUR001-301 and DUR001-302

Was a list of clinical investigators provided:	Yes
Total number of investigators identified: **924**	
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**	
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**	
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **Not Applicable**	
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **0**	
Is an attachment provided with the reason: **Not Applicable**	

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[6]

There were no investigators who are sponsor-employee or who had disclosable financial arrangements.

6 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf

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

/s/

DMITRI IARIKOV
03/31/2014

JOHN J ALEXANDER
04/03/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21883 **Applicant: Durata Therapeutics, Inc** **Stamp Date: 09/26/2013**

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

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			NA	505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? **Study Number**: VER001-5 **Study Title**: A Phase 2, Pilot, Randomized, Open-Label, Multi-Center Study to Evaluate the Safety and Efficacy of Dalbavancin Versus Investigator/Physician-Designated Comparator in Skin and Soft Tissue Infection **Sample Size**: N=61 (41 in the dalbavancin and 21 in comparator arm) **Arms**: Arm 1:Dalbavancin single i.v. dose of 1100 followed, one week later, by a second	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	i.v. dose of 500 mg Arm 2: Dalbavancin 1000 mg followed, one week later, by a second i.v. dose of 500 mg Arm 3: investigator-designated comparator antibiotics for up to 21 days. Location in submission: Module 5.3.5.4				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 DUR001-301 Indication: Acute Bacterial Skin and Skin Structure Infections Pivotal Study #2 DUR001-302 Indication: Acute Bacterial Skin and Skin Structure Infections	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			NA	Study drug was administered for up to 2 weeks
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			NA	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			NA	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Dmitri Iarikov, MD	October 30, 2013
Reviewing Medical Officer	Date
John Alexander, MD	October 30, 2013
Clinical Team Leader	Date

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/s/

DMITRI IARIKOV
10/31/2013

JOHN J ALEXANDER
11/01/2013

NDA 21-883: Dalbavancin – Complete Response to Approvable Letter (6/20/06)
Janice Pohlman, MD, Medical Officer

BACKGROUND

Vicuron Pharmaceuticals, Inc. filed an original new drug application (NDA) for Dalbavancin powder for injection on December 21, 2004. Based on the clinical review (Clinical Efficacy by Janice Pohlman, M.D. and Integrated Safety Summary by Menfo Imosili, M.D.), the recommendation was made for approval of dalbavancin for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* including methicillin-resistant strains (MRSA), *Streptococcus pyogenes*, and *Streptococcus agalactiae* (see previous clinical reviews in DFS, September 21, 2005). On September 21, 2005, an approvable letter was issued to the Sponsor listing the deficiencies requiring response prior to approval. There were two deficiencies listed; the first was a chemistry and manufacturing issue related to proposed intermediate storage and the second to FDA and Sponsor agreement on final labeling.

On December 20, 2005, Pfizer, Inc. submitted a complete response to the approvable letter on behalf of its subsidiary, Vicuron Pharmaceuticals. There was no additional clinical data submitted with this response. Clinical input for the response included providing the Applicant with information regarding derivation of VER001-9 study results contained within the analysis tables in the clinical studies section of the label proposed by FDA. The clinical review also contained a brief summary for study VER001-16, a randomized, unblinded Phase 3 study in patients with suspected (or proven) MRSA-related SSSI, initiated by the Applicant after the ongoing Phase 3 study of uncomplicated skin and skin structure infection (uSSSI) study (VER001-8) was noted to have higher than anticipated enrollment of patients with MRSA infection. While Study VER001-16 provided information regarding efficacy of dalbavancin in the treatment of patients with SSSI, particularly in patients with infections caused by MRSA, the study was not extensively reviewed and analyzed by the FDA for efficacy due to multiple study design issues (see previous clinical review of Complete Response in DFS, June 2, 2006). Clinical microbiology breakpoints were also established and agreed upon by FDA and Sponsor for proposed labeling during this review cycle. The CMC review of the intermediate storage issue cited in the September 21, 2005 approvable letter was satisfactory and on June 21, 2006, a second approvable letter was issued with listed deficiencies related to high bacterial endotoxin levels discovered in the active pharmaceutical ingredient (API) and drug product (DP) lots. .

On June 20, 2007, Pfizer, Inc. submitted a complete response to the June 21, 2006 approvable letter on behalf of its subsidiary, Vicuron Pharmaceuticals. No additional clinical data was submitted with this response. However, on July 7, 2007 an information request was sent by FDA to Pfizer requesting that the Sponsor provide justification for the (b) (4) non-inferiority (NI) margin used in the Phase 3 SSSI studies (VER001-8 and VER001-9), as well as requesting that the Sponsor submit a proposal for a thorough QT study, now being recommended for all new molecular entity (NME) NDAs. This clinical

review includes discussion provided by the Sponsor regarding justification for the use of the specified NI margin of (b) (4) in VER001-9 (the cSSSI study).

NI Margin Justification

At a meeting of the Anti-Infective Advisory Committee on September 12, 2006, FDA discussed the evolution of its understanding of clinical trial design and the use of NI studies in drug development. More rigorous justification of selected NI margins based on previously conducted superiority studies (placebo- or active-controlled), published literature, and other relevant scientific data is now being required. Based on this discussion the Sponsor was requested to provide information regarding justification for the use of the (b) (4) NI margin in the previously conducted cSSSI (VER001-9) and uSSSI (VER001-8) studies.

At the End of Phase 2 meeting on October 30, 2002, FDA recommended the Sponsor select a NI margin for the Phase 3 skin and skin structure infection (SSSI) studies sufficient to demonstrate robust results and advised that a larger sample size and smaller margin would provide stronger evidence of efficacy in the NDA package. The FDA and Sponsor agreed that one adequate and well-controlled trial in uSSSI (VER001-8), one adequate and well-controlled trial in cSSSI (VER001-9), and one supportive non-US study in cSSSI (VER001-17) demonstrating efficacy and safety would be adequate to support approval of dalbavancin for treatment of SSSIs.

At the pre-NDA meeting between FDA and the Sponsor on May 11, 2004, the discussion focused on content and format for the electronic submission of the NDA and the appropriate integration of study populations for safety and efficacy analyses. On October 29, 2004, a follow-up pre-NDA Meeting (Clinical Review Meeting) was held. The primary focus of the meeting was to discuss the results of VER001-9 (the cSSSI study), particularly the difference in the point estimates for the response rate difference (dalbavancin – linezolid) in the ITT and CE analyses (b) (4) The Sponsor noted that they were seeking approval for the use of dalbavancin in the treatment of cSSSI only, believing that the use of dalbavancin was most appropriate in the treatment of serious infections (b) (4) The FDA agreed that the data from Study VER001-8 appeared to support findings from Study VER001-9 and with the overall approach to use results from Study VER001-8 in a supportive fashion.

Brief Review of Clinical Study Results

Two Phase 3 clinical trials were conducted by the Sponsor for the determination of the efficacy of dalbavancin in the treatment of SSSI; VER001-8 in uSSSI and VER001-9 in cSSSI. The FDA and Sponsor had previously agreed that the efficacy results from VER001-9 would be the single pivotal trial considered for approval and that results from VER001-8 would be used in supportive fashion.

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/s/

Janice Pohlman
12/11/2007 08:13:39 PM
MEDICAL OFFICER

BACKGROUND

Vicuron Pharmaceuticals, Inc. filed an original new drug application (NDA) for Dalbavancin powder for injection on December 21, 2004. Based on the clinical review (Clinical Efficacy by Janice Pohlman, M.D. and Integrated Safety Summary by Menfo Imosili, M.D.), the recommendation was made for approval of dalbavancin for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* including methicillin-resistant isolates, *Streptococcus pyogenes*, and *Streptococcus agalactiae* (see previous clinical reviews in DFS, September 21, 2005). On September 21, 2005, an approvable letter was issued to the Applicant listing the deficiencies requiring response prior to the approval. There were two deficiencies listed; the first was a chemistry and manufacturing issue related to proposed intermediate storage and the second related to agreement on final labeling.

On December 20, 2005, Pfizer Inc. submitted a complete response to the approvable letter on behalf of its subsidiary, Vicuron Pharmaceuticals. There was no additional clinical data submitted with this response. Therefore, the clinical review of this response consisted of review of the Applicant's proposed labeling.

LABELING REVIEW: CLINICAL EFFICACY (Pfizer resubmission: 12/20/05)

INDICATIONS AND USAGE

(b) (4)

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(b) (4)

[redacted]

MEDICAL OFFICER CONCLUSIONS AND RECOMMENDATIONS

1. Based upon the previous clinical efficacy and safety reviews (September 19, 2005) for dalbavancin, it is recommended that dalbavancin be approved for the treatment of adult patients with cSSSI caused by *Staphylococcus aureus* including methicillin-resistant isolates, *Streptococcus pyogenes* and *Streptococcus agalactiae*.

2. The results of the subgroup analysis of success rates in patients with cSSSI in Study VER001-16 (b) (4) do not provide additional data from that previously reviewed in Study VER001-09. Study VER001-09 was a randomized, double-blind, active comparator controlled trial assessing the efficacy of dalbavancin relative to linezolid in the treatment of patients with cSSSI. (b) (4) In the pre-NDA meeting briefing package, the Applicant indicated that VER001-16 was a supportive rather than a pivotal study and therefore the Study was not extensively reviewed and analyzed by the FDA for efficacy.
3. The following changes to the Applicant's proposed labeling, as discussed (b) (4)

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/s/

Janice Pohlman
6/2/2006 02:47:29 PM
MEDICAL OFFICER

Sumathi Nambiar
6/2/2006 02:54:10 PM
MEDICAL OFFICER

Supplementary Safety Review of Dalbavancin
Medical Officer: Menfo A. Imoisili, MD, MPH.
Date: May 17, 2006

Background

Dalbavancin is a novel second-generation semisynthetic lipoglycopeptide, related to the glycopeptides, teicoplanin and vancomycin[1]. Unlike the latter two agents, it has a long half-life of 9-12 days.[2] It is an intravenously administered drug with a recommended regimen for adults of 1000 mg on the first day of therapy (Day 1), followed a week later (Day 8) by 500 mg with dose adjustment for severe renal compromise. Dalbavancin has not been studied in pediatric population.

The NDA application (#21883) for the indication of complicated skin and skin structure infection (SSSI) was submitted to FDA on December 21, 2004. On completion of its review, an Approvable Letter was issued to Pfizer/ Vicuron Pharmaceuticals on September 21, 2005.
In the review of the application, significantly altered glucose homeostasis (severe hypoglycemia and hyperglycemia) and liver enzyme elevations (ALT > 20x ULN) occurring either exclusively or predominantly in dalbavancin-treated patients emerged as the two major safety concerns. (b) (4) . The review will focus on the differences between the Agency and the Sponsor concerning glucose homeostasis (b) (4)

(b) (4)

(b) (4)

The Agency's response to this submission included an agreement to a teleconference dialogue (scheduled for May 1, 2006), and written responses to the Sponsor's queries contained in their December 20, 2005 submission (see Appendix 2). In addition, the Agency requested of the Sponsor to provide evidence of investigations conducted by them to determine the potential mechanisms for interaction between dalbavancin and glucose homeostasis. In response, the Sponsor provided preclinical study reports (in rats and dogs) prior to the May 1, 2006 teleconference meeting which they also discussed at the meeting (Appendix 3).

Sponsor's Pre-clinical evidence against dalbavancin's relationship to dysglycemia (summarized).

1. Non-clinical toxicity studies of 3 months duration in the dog and rat, conducted by the company, have shown no alterations in serum glucose levels.

2. The pancreatic acinar cell vacuolization, degeneration and apoptosis observed in rats treated with dalbavancin were not associated with changes in the endocrine pancreas, including the islet β-cells.

3. Unlike the fluoroquinolones (e.g. gatifloxacin) known to cause dysglycemia, dalbavancin does not contain a pharmacophore whose activity characteristic is associated with dysglycemias. In addition, the potential for gatifloxacin effects on pancreatic beta cell function was predicted by pre-clinical toxicology studies in which pancreatic beta cell vacuolation was observed by light microscopy in three species: rats, dogs, and monkeys.

Review of glucose homeostasis

The safety issues in this second review cycle are: 1.) whether there is an interaction between dalbavancin and glucose homeostasis, or whether an association exist between the receipt of dalbavancin and dysglycemia; 2.) if there is, how can it be established? 3.) whether all the hypoglycemic patients (serum glucose level < 40 mg/dL) were truly asymptomatic or whether the clinical symptoms were inadvertently missed.

With regard to the last question, patient # 09017006 was reported as having a serious AE (SAE). He had been reported asymptomatic when his serum glucose was 38 mg/dL two days earlier but when he was found on the floor two days later, a serum glucose check was 54 mg/dL.
He was also reported to be overdosed with two non-glucose –lowering drugs. The case narrative was given as follows.

AE Narrative: Patient 09-017-006, a 64-year-old Caucasian male, participated in 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 Soft Tissue Infections with Suspected or Confirmed Gram-Positive Bacterial Pathogens. The patient's medical history is significant for chronic obstructive pulmonary disease, coronary artery disease, myocardial infarction, total hip replacement, cachexia, malnutrition, hypoglycemia, osteoporosis, compression fractured L3, chronic pain syndrome of the back and left hip, numbness in left foot and weakness in left leg. The patient was hospitalized on (b) (6) due to unexplained weight loss (30 pounds in six months). On (b) (6) a biopsy of his left sacrum was performed. An abscess and cellulitis developed.

On (b) (6), an aspiration of the abscess revealed methicillin-resistant *Staphylococcus aureus*. He received blinded IV study medication (dalbavancin) beginning on (b) (6). The patient was discharged from the hospital on 1 (b) (6) On (b) (6) the patient experienced hypoglycemia (glucose 38). On (b) (6), he was found on the floor.

The patient was admitted to the hospital for dehydration, malnutrition and hypoglycemia (glucose 54). The patient was disoriented with jumbled speech and right sided chest pain, left hip and back pain. The patient was started on dextrose 50 % and normal saline for dehydration. A repeat glucose was 163. Upon further evaluation it was determined that the patient accidentally overdosed on tramadol and orphenadrine. The patient recovered from the event on (b) (6) and was discharged two days later. The investigator concluded the event to be unrelated to treatment with study medication.

Medical History: Chronic Obstructive Pulmonary Disease, Coronary Artery Disease, Myocardial Infarction with Cardiac Stent (Apr-2003), Total Hip Replacement (x3), Cachexia, Malnutrition, Hypoglycemia, Osteoporosis, Compression Fractured L3, Chronic Pain Syndrome of the Back and Left Hip, Numbness in Left Foot, Weakness in Left Leg Since 1988.

Case Discussion

Summary

(b) (6) Hospitalized.
Received first dose of dalbavancin.
Discharged from the hospital.
Hypoglycemia (serum glucose = 38) on day 8; received dose # 2 (dalbavancin).
Found on the floor. Re-hospitalized (serum glucose = 54) on day 10 from dose # 1; day 2 from dose #2 (dalbavancin).

***Table 1: Serum Glucose Profile of Patient* # 09017006**

PTID	*Dalbavancin Dose received*	*Baseline*	*Day 8*	*Day 10*	*EOT*	*TOC*	*Diabetes mellitus*
09017006	*2 doses*	*98*	*38*	*54*	*92*	*62*	*No*

MO comments

The case of this 64-year-old, non-diabetic man underscores DAIOP's concern regarding the potential for dalbavancin to cause dysglycemia (in this case, hypoglycemia). In the literature, the possible causes of hypoglycemia in adults are numerous. Of significance, this patient had a medical history of cachexia, malnutrition and unexplained weight loss (30 lb in 6 months). No

reported history of chronic alcohol usage that could have depleted his liver reserve of carbohydrates, nor acute alcohol ingestion, often associated with serum glucose depression. Other medications with serum glucose lowering potential were not reported in the patient, nor relevant to his health. For example, he had not received insulin (no history of diabetes mellitus), quinine (for malaria or babesiosis treatment), etc. It was reported, however, that he accidentally ingested overdose amounts of tramadol, an analgesic, and orphenadrine, used for the relief of musculoskeletal discomfort and pain. According to the Physician Desk Reference (PDR), serious potential consequences of tramadol overdose comprise central nervous system (CNS) and respiratory depression and death. The PDR also reports that some patients may report light-headedness, dizziness or syncope with orphenadrine, as well as anxiety, tremors, confusion and anticholinergic adverse events. No hypoglycemia is reported with any of the two drugs.
The third drug in the patient's system at the time he was found on the floor was dalbavancin. He received the first dose 10 days earlier. He received a second dose two days earlier, the day he had a serum glucose of 38 (see Table 1).
Symptoms of acute or subacute hypoglycemia can include sweating, tremors, palpitations, anxiety, dizziness, slurred speech, disorientation, headache, blurred vision, and with further neurologic deterioration, convulsion, coma and, rarely, death.
What could have caused this patient's hypoglycemia? What could have caused his reported disorientation and jumbled speech?

The 5 patients with hypoglycemia reported in dalbavancin studies were reported to be asymptomatic. This patient (09017006) was one of them. He had serum glucose of 38 mg/dL. His glucose level drawn when he was found on the floor was 54 mg/dL. This level only represented one time point. His serum glucose nadir could have only been 54 or less; the exact value is unknown. Being "disoriented with jumbled speech" could have resulted from his drug overdose, his hypoglycemia, or a combination. The cause of his hypoglycemia cannot be specifically identified. But dalbavancin can not be ruled out, given that he had documented hypoglycemia of 38 two days earlier, presumably with no tramadol and/or orphenadrine (or their overdose amounts) on board, and in the context of three other non-diabetic cases who received dalbavancin developing a similar degree of hypoglycemia in the Phase 3 studies.

As shown by the Sponsor, the pre-clinical studies so far conducted have shown no involvement of the beta cells of the islets of Langerhans in rats and dogs that received dalbavancin. Nor were dysglycemia recorded or reported in these animals. Could dalbavancin cause dysglycemia by some other mechanism then? Is there an appropriate moment following the receipt of dalbavancin to check serum glucose to document more dysglycemic cases that may have been missed first time around? Most of the 1267 subjects/patients who received dalbavancin developed no dysglycemia. What is/are the predisposing factor(s) for developing dysglycemia in those who receive dalbavancin, if indeed the phenomenon is real? Is it idiosyncratic?

These issues were discussed at a teleconference with the Sponsor on May 1, 2006.

DAIOP's Post Teleconference Step taken

Given that dysglycemia has been identified in dalbavancin- treated humans, but not in dalbavancin-treated rats and dogs studied, concerning the possible mechanisms for the

dysglycemia, DAIOP recommended that a different animal, physiologically closer to humans whose study could be more instructive be identified. Accordingly, a formal consult was sent from DAIOP to the Division of Endocrine and Metabolic Products of FDA on May 5, 2006, seeking advice on future animal studies/in vitro studies and clinical studies that may help determine any possible association between receipt of dalbavancin and development of dysglycemia.

Final Review Comments on dysglycemia in human dalbavancin recipients

The relationship between dysglycemia and the receipt of dalbavancin remains a suspicion based on the occurrence at all, the number, and the severity of the phenomenon, as well as the imbalance across study arms. The number may not be a large one. But they were found when they were not sought or expected. Could a more aggressive search for dysglycemia in a future study yield a larger number? At the end, the exploration may yield nothing. But, if the phenomenon is real, any further exploration done to uncover and characterize this issue would be worthwhile. As dalbavancin uniquely has a long half-life, unlike the other products in its class, any information further obtained to establish a stronger association would be clinically beneficial. It would be clinically beneficial to Prescribers. As to whether the company plans to conduct studies in humans with a more aggressive surveillance approach, at least the issue has been discussed. Perhaps, results from further animal studies might weigh on that decision. Of note, four of the five cases with profound hypoglycemia (serum glucose < 40 mg/dL) reported in the Phase 3 trials occurred at the end of treatment (EOT). Post-marketing surveillance should also provide additional information – either way.

ADVERSE REACTIONS

In this section of the Sponsor's May 5, 2005 proposed label, (b) (4)

MO Comment

MO does not recommend the approach the Sponsor has taken to present AEs in this section; The MO makes the following recommendations:

1. Studies Pooled for AE evaluation

In keeping with our labeling practice of anti-infective drug products in recent years and consistent with the principles outlined in the "Guidance for Industry, Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (January 2006)", *we recommend that, for labeling purposes in this section of the label, AEs be derived from those reported in Phase 3 studies.* (b) (4)

(b) (4)

2. Treatment-related AEs versus all-causality AEs

The agency's current thinking on this issue is that common AE listing should be derived from "all causalities" AEs reported at or above a specified rate that is appropriate to the drug safety database. Determination of treatment –related AEs is more difficult, is often subjective and the results may vary from person to person. Therefore, DAIOP has proposed to put back the "all causality" AEs in ≥ 2% of Phase 3 patients in this section of the label.

(b) (4)

Other Proposed Changes

The label also contains the following statements, words, phrases, numbers, or rates which DAIOP changed or modified to maintain cohesion, preserve meanings of sentences, or give rates in accordance with the changed denominator number (Phase 3) and the AE causality determination based on "all causalities" rates. The Sponsor's rates were crossed out and replaced

by DAIOP's recalculated value underlined, or words/phrases were substituted or spelling corrected. Based on these, the following (blue text) changes were made in the label.

Label

(b) (4)

[redacted]

Conclusions

The initial review of dalbavancin (NDA #21883) was completed on September 21, 2005. This second cycle supplementary safety review (b) (4)

[redacted]

[redacted] (b) (4), and following discussions with the dalbavancin review team, the reviewer reached the following safety conclusions [redacted] (b) (4).

1. In the Phase 3 studies, of the 5/1045 (0.5%) dalbavancin-treated patients compared to none in the comparator-treated patients had severe hypoglycemia (serum glucose $\leq$ 0.6 x LLN and $\geq$ 0.4 fold decrease). One was receiving insulin for diabetes mellitus.

2. Also in the Phase 3 studies, 7/1045 (0.7%) dalbavancin-treated patients compared to 1/518 (0.2%) comparator-treated patients had severe hyperglycemia (serum glucose elevations $\geq$ 3 x ULN and $\geq$ 3 fold increase). Five of the patients who received dalbavancin were diabetic and on insulin.

3. The relationship between the receipt of dalbavancin and the development of dysglycemia should be further explored.

4. The MO recommends that common AE rates under the Adverse Reaction section be calculated using the number of patients in Phase 3 studies as the denominator.

5. The MO further recommends that common AE report tabulations be done as "all causality" AEs reported at or above a specified rate that is appropriate to the dalbavancin-treated versus comparator-treated patient database ($\geq$2% chosen for this review) in the Phase 3 studies.
6. Other MO-proposed changes include deletions of [redacted] (b) (4)

References

1. Kahne D, Leimkuhler C, LU W, Walsh C. Glycopeptide and Lipoglycopeptide Antibiotics. *Chem. Rev*. 2005; 105,425-448

2. Mushtaq S, Warner M, Johnson AP, Livermore DM. Activity of dalbavancin against staphylococci and streptococci, assessed by BSAC and NCCLS agar dilution methods. *J Antimicrob Chemother*. 2004 Sep;54(3):617-20. Epub 2004 Aug 20.

APPENDIX 1

Regulatory Affairs
Pfizer Inc
235 Fast 42nd Street 605/5/16
New York, NY *10017*
Tel 212 573 4471 Fax 212 *857* 3558
Email srulee@pfizer.com

Pfizer Pharmaceuticals Group

Elina Sruievitch - Chin
Director Team Leader
Worldwide Regulatory Strategy

December 20, 2005

Janice Soreth, MD, Director
Division of Anti-Infective and Ophthalmologic Products
OAP / CDER / FDA
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: NDA2 1-883 (b) (4) (dalbavancin for Injection)

COMPLETE RESPONSE TO APPROVABLE LETTER

Dear Dr. Soreth:

Reference is made to the NDA2 1-883 (b) (4) "a (dalbavancin for Injection), submitted to the Division of Anti-Infective and Ophthalmology Products on December 21, 2004. Further reference is made to the approvable letter issued on September 21, 2005 and the "Advice Letter" dated October 4, 2005.
This submission contains a complete response to the Approvable letter and addresses the points outlined in the advice letter. The following is a summary of items included in this response:

CHEMISTRY MANUFACTURING AND **CONTROLS**
• Isolated Intermediate Storage
• Master Cell Bank/Working Cell Bank
• Specificity of Regulatory HPLC Assay
• Request for Samples

LABELING
Pfizer has updated the proposed labeling based on the s draft dated September 21,

2005 to address the Division's comments included in that draft.
We enclose two versions of the revised annotated USPI: one version showing the proposed revisions and a clean version with the revisions incorporated.

We have made revisions to the following sections of the label: **DESCRIPTION, MICROBIOLOGY, PRECAUTIONS, ANIMAL PHARMACOLOGY, ADVERSE REACTIONS, PREPARATIONAND ADMINISTRATION, COMPATIBILITY, STABILITY AND STORAGE, HOW SUPPLIED** and **CLINICAL STUDIES.**

We enclose a brief summary in support of the revisions we have made to the **Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy** subsections as well as to the **ANIMALPHARMACOLOGY** section.

We also include **a** summary to support the proposed revisions to the **MICROBIOLOGY** Section and provide additional information on anaerobic susceptibility testing as requested in your advice letter.

Glucose Homeostasis
We would like to request a dialog with the Division in order to gain clarity around their perspective relative to glucose homeostasis, as well as any corresponding proposed wording and its placement in the label.

Finally, we note the Division's addition of Tables 8, 9 and 10 in the **CLINICAL STUDIES** section and seek insight as to how these tables were derived.
The CD Rom has been scanned for viruses using McAfee Virus Scan Enterprise Version 7.1.0 and is virus free. This electronic submission is approximately 5.60 MB in size.

Should any questions arise concerning this submission, please do not hesitate to contact me at 212-733-4471.

Sincerely,
Elina Srulevitch-Chin

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APPENDIX 3

RESPONSE TO THE FDA COMMENTS (facsimile dated March 16, 2006)
GLUCOSE HOMEOSTASIS

QUERY
Please provide any evidence you have regarding investigations conducted to determine potential mechanisms for interaction between dalbavancin and glucose homeostasis. In the pre-clinical studies submitted to the Agency by Vicuron Pharmaceuticals, rats and dogs that received daily dalbavancin for up to 3 months duration, vacuolization, degeneration and apoptosis involving the acinar cells of the pancreas were reported. The significance of these events is unclear. It is also unclear whether these events can occur in humans. If they can, their clinical significance is probably yet to be elucidated.

RESPONSE
Preclinical considerations
Non-clinical toxicity studies of 3 months duration in the dog and rat have shown no alterations in serum glucose levels. In the dog study (Study #168-003), there were no treatment-related lesions of the pancreas (islets or acini). In the rat study (Study #168-002), the study pathologist described microscopic findings of trace to mild "Vacuolation (Acinar Cell Degeneration)" at all doses (5, 10, and 40 mg/kg/day). The peer review pathologist for the rat study used the terms "Degeneration Vacuolar Acinar Cells" and "Apoptosis" to describe the pancreatic acinar findings, but acknowledged that these terms probably represented a continuum of the same process described by the study pathologist. Internal review of the pancreas slides at Pfizer confirmed that these apparent differences reflected terminology differences and that the acinar change consisted of vacuoles containing cellular debris (a common morphologic response to sublethal pancreatic acinar damage). Zymogen content and pancreatic acinar volume were preserved. Treatment-related microscopic findings in the rat pancreas were limited to the exocrine pancreas-there were no treatment-related findings in pancreatic islet cells in rats at any dose. Based on these non-clinical studies, there is no evidence that dalbavancin has any effect on glucose homeostasis.

Acinar cell vacuoles similar to that seen in dalbavancin-treated rats was also observed in rats treated with teicoplanin, a lipoglycopeptide related to dalbavancin. The acinar vacuoles associated with dalbavancin probably represented auto-phagolysosomes (as they were determined to be by electron microscopy in teicoplanin-treated rat pancreas). The pancreatic acinar cell vacuoles observed in rats treated with dalbavancin and teicoplanin were not associated with either changes in the endocrine pancreas or with more advanced treatment-related exocrine pancreatic morphologic changes (e.g. acinar atrophy, necrosis, inflammation, fibrosis). The acinar cell vacuolar changes were not associated with any apparent effects on exocrine pancreatic function (i.e. synthesis and secretion of digestive enzymes including trypsin, chymotrypsin, lipase, and amylase). Therefore, in the absence of associated effects on the endocrine pancreas (and particularly ® cells, that synthesize and secrete insulin), there is no pathophysiological support for an association between pancreatic acinar cell vacuolation or other acinar cell changes and effects on glucose homeostasis.

The fluoroquinolones are the antibiotic class most commonly associated with clinical dysglycemia. In the US, increasing reports of adverse effects on glucose homeostasis have resulted in several label changes for the fluoroquinolone antibiotic gatifloxacin (Park-Wyllie et al, 2006). The nonclinical findings for dalbavancin are distinct from findings of gatifloxacin (Table 1). The potential for gatifloxacin effects on pancreatic endocrine (beta cell) function was predicted by preclinical toxicology studies in which pancreatic beta (®) cell vacuolation was observed by light microscopy in three species: rats, dogs, and monkeys (Tequin$_{v}$ Pharm/Tox Review). The corresponding ultrastructural changes in these vacuolated ® cells included dilated/vesiculated rough endoplasmic reticulum and/or decreased secretory granules. Changes in serum glucose or insulin levels were also sporadically observed in some toxicology studies with gatifloxacin, but there was no consistent association with the ® cell morphologic effect.

Dalbavancin is structurally related to vancomycin (a tricyclic glycopeptide antibiotic with no dysglycemia association) and is chemically distinct from the fluoroquinolones. It therefore does not contain a pharmacophore that has previously been associated with dysglycemias, and there are no grounds on which a class effect on glucose homeostasis would be expected.

In summary, no pancreatic ® cell morphologic effects of any kind were observed at any dose level in the toxicology studies of dalbavancin in rats and dogs. No treatment-related pancreatic changes of any kind were observed in dalbavancin-treated dogs. Dalbavancin is not a member of a pharmacophore class associated with clinical dysglycemia. There is consequently no evidence to suggest a treatment-related effect of dalbavancin on glucose homeostasis.

Table 1. Comparison of Treatment-Related Morphologic Pancreatic Effects in Preclinical Toxicology Studies with Gatifloxacin, Dalbavancin, and Teicoplanin

	Gatifloxacin (a)		**Dalbavancin (b-g)**		**Teicoplanin (h)**	
Species	**Endocrine**	**Exocrine**	**Endocrine**	**Exocrine**	**Endocrine**	**Exocrine**
Rat	LM: β cell vacuolation at 810 mg/kg/day in 1-month oral study; ≥ 120 mg/kg/day in 6-month oral study; and at 0.8%i of the diet for 3 months. A 3-fold increase in glucose at 0.8% in feed relative to control was reported in the in-feed study but not the oral studies. EM: Dilatation of rough endoplasmic reticulum (RER)	None reported	None LM: Acinar cell vacuolation at ≥ 5 mg/kg/day in 4-week and 3-month IV studiesj with no glucose changes EM: Not performed	None	None LM: Acinar cell vacuolation at doses up to 80 mg/kg/day IV for 1 month and up to 150 mg/kg/day EM: autolysosomes	None reported
og	LM: β cell vacuolation at ≥20 mg/kg in 1-month oral study and at ≥12 mg/kg/day in 6-month oral study EM: Dilatation of RER Acinar atrophy at 60/40 mg/kg in 1-month oral study and at ≥ 12 mg/kg in 6-month oral study	None	None	None	None	None reported
Cynomolgus Monkey	LM: Not described EM: Vesiculation of RER and ↓ secretory granules in βcells at ≥15 mg/kg/day) in 5-month oral study	None reported	No toxicity studies in primates were performed with dalbavancin		No toxicity studies in primates were performed with teicoplanin	

a Tequin Pharm/Tox Review.
b Peano S. 1999a. Study (b) (4) 971096.
c Peano S. 1999b. Study 980831.
d Peano S. 1999c. (b) (4) 971098.
e Peano S. 1999d. Study (b) (4) 980779.
f Seng J. 2004a. Study 168-002.
g Seng J. 2004b. Study 168-003.
h Goldstein BP et al. 1994.
i Corresponds to 636 mg/kg and 547 mg/kg in male and female rats, respectively
j Other acinar changes (focal degeneration, atrophy, hypertrophy, decreased secretory material), focal islet degeneration, islet hyperplasia, hemorrhage and pancreatic inflammation were observed sporadically in rats either in the control group only or at comparable incidence in the control group and/or one or more treated groups without dose dependence. These changes were not considered treatment-related.
k Acinar cell degeneration was reported, in conjunction with vasculitis, in one male dog at 40 mg/kg that was euthanized in moribund condition on day 57 of the 90-day study. No other pancreatic changes were observed in dogs on this study and in this case the effect was considered related to the moribund condition of the animal rather than dalbavancin treatment. Focal, slight pancreatic acinar atrophy was observed in one male dog at 40 mg/kg in one of the two 4-week studies in dogs (Study (b) (4) 980779). Focal or multifocal, slight pancreatic inflammation was observed in three female dogs in the control group on the same study. None of these changes was considered treatment-related.
LM = light microscopy; EM = electron microscopy

Medical Officer supplementary safety review of NDA # 021883 (Dalbavancin)

Clinical considerations
In Phase 3 studies, hyperglycemia (PCS and PCSC) was observed in 7/1045 (0.7%) of dalbavancin-treated patients and 1/518 (0.2%) of comparator-treated patients. Hypoglycemia (PCS and PCSC) was noted in 5/1045 (0.5%) of dalbavancin-treated patients and 0/518 comparator-treated patients.

In Phase 3, hyperglycemia was reported as an adverse event (all causality) in 15/1045 (1.4%) of dalbavancin-treated patients and in 8/518 (1.5%) of comparator-treated patients. Hypoglycemia was reported in 13/1045 (1.2%) of dalbavancin-treated patients and in 9/518 (1.7%) of comparator-treated patients.

Increased blood glucose was reported as an adverse event in 6/1045 (0.6%) in dalbavancin-treated patient and in 4/518 (0.8%) in comparator-treated patients. Diabetes mellitus was reported as an adverse event in 2/1045 (0.2%) of dalbavancin-treated patients and in 1/518 (0.2%) of comparator-treated patients. Inadequate control of diabetes mellitus was reported in 2/1045 (0.2%) of dalbavancin-treated patients.

The twelve clinical cases of laboratory defined hyper- and hypoglycemia recorded in the dalbavancin clinical program have previously been presented to DAIOP (Vicuron Correspondence –Response to FDA Request for Information. 24 August 2005). On examination of the individual case report forms, we observe the following:

- All twelve patients were asymptomatic including hypoglycemic patients.
- The blood glucose levels in two patients (08-029-003 and 09-009-023; reported as hypoglycemic and hyperglycemic, respectively) can be discounted due to lab or sampling error.
- Various confounding factors that may have contributed to either the hypoglycemic or hyperglycemic state were present. These factors included diabetes mellitus, poor glycemic control, obesity, infection, cancer, malnourishment or concomitant medications.

Dysglycemias tend to occur in patients with numerous risk factors and in populations with and without diabetes mellitus (Owens et al, 2005). Severe infections can predispose patients to both hyperglycemia and hypoglycemia (McMahon et al, 1995). In patients with diabetes mellitus, the presence of infection causes an even greater derangement in glucose metabolism than in the non-diabetic patient. In addition to diabetes mellitus, risk factors for hyperglycemia include trauma, emotional stress, older age, total parenteral nutrition, stroke, and medications including exogenous corticosteroid use (Cely et al, 2004; Gaglia et al, 2004; Gavin et al, 2004; McGuinness, 2005; Powers, 2005).

Furthermore, blood glucose concentrations in patients with and without diabetes fluctuate on a daily basis. In adults (50-74 years) without a history of diabetes, the intra-individual variability (CV) of fasting and 2-hour postprandial blood glucose concentrations was 6.4% and 16.7%, respectively (Mooy et al, 1996). Overall, the reported variability (%CV) of blood glucose concentrations in patients with diabetes (type 1 and type 2) ranges from 15% to 41% (Derr et al, 2003; Moberg et al, 1993; Murata et al, 2004; Ollerton et al, 1999; Muggeo et al, 2000).

The incidence of hypoglycemia and hyperglycemia in the population of patients with complicated skin and soft structure infection (cSSSI) is unknown. No data has been published on dysglycemias in patients with cSSSI treated with either vancomycin or teicoplanin.

Conclusions

In summary, no pancreatic ® cell morphologic effects of any kind were observed at any dose level in the toxicology studies of dalbavancin in rats and dogs. No treatment-related pancreatic changes of any kind were observed in dalbavancin-treated dogs. Dalbavancin is not a member of a pharmacophore class associated with clinical dysglycemia. There is consequently no evidence to suggest a treatment-related effect of dalbavancin on glucose homeostasis. The frequencies of glucose-related adverse events were similar in dalbavancin and comparator-treated patients. Additionally, confounding factors likely to contribute to the development of dysglycemia, were present in the majority of the clinical cases of laboratory hypo- or hyperglycemia. Based on these data, the Sponsor concludes that there are no preclinical or clinical signals predictive of an effect of dalbavancin on glucose homeostasis

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Peano S. 4-week repeated dose toxicity study in Sprague Dawley Crl:CD (SD) BR rats treated with the test article BI 397 administered by intravenous route at the doses of 0, 10, 20, 40 and 80 mg/kg/day followed by 4 weeks of recovery. (b) (4) (b) (4) Study (b) (4) 980831.

Peano S. Study 4-week repeated dose toxicity study in Beagle dogs treated with the test article BI 397 administered by intravenous route at the doses of 0, 5, 10, 20 and 40 mg/kg/day, followed by 4 weeks of recovery at the dose of 20 mg/kg/day. (b) (4) (b) (4) . (b) (4) 971098.

Peano S. 4-week repeated dose toxicity study in Beagle dogs treated with the test article BI 397 administered by intravenous route at the doses of 0, 10, 20 and 40 mg/kg/day, followed by 4 weeks of recovery at the dose of 40 mg/kg/day, with an additional group of animals treated at 60 mg/kg/day. (b) (4) . Study (b) (4) 980779.

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Tequin® Pharm/Tox Review: http://www.fda.gov/cder/foi/nda/99/21061_Tequin.htm

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/s/

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SAFETY REVIEW

Application Type	NDA
Submission Number	21883
Submission Code	
Letter Date	December 20, 2004
Stamp Date	December 21, 2004
PDUFA Goal Date	September 21, 2005
Reviewer Name:	Menfo Imoisili, MD, MPH
Review Completion Date	September 21, 2005
Established Name	Dalbavancin
(Proposed) Trade Name	Dalbavancin
Therapeutic Class	Antibiotic
Applicant	Vicuron Pharmaceuticals Inc.
Priority Designation	{S}
Formulation	Intravenous
Dosing Regimen	1000 mg on day 1; 500 mg on Day 8
Indication	Complicated skin and skin structure infections
Intended Population	Adults

Table of Contents

7 INTEGRATED REVIEW OF SAFETY

This is the safety review for NDA 21883. For the executive summary and efficacy review , please refer to the review by y Dr. Janice Pohlman.

7.1 METHODS AND FINDINGS

General information

This safety review consists of safety data on all 1267 subjects who received 1270 courses of dalbavancin in seven Phase1, two Phase 2 and three Phase 3 studies. The additional 3 courses, according to the sponsor, resulted from the 3 subjects in Study VER001-11 who were enrolled twice (as permitted by the protocol) and received 2 separate courses of dalbavancin. One of the Phase 1 studies conducted was not included in the sponsor's integrated database. This study (VER001-3) was terminated early due to the sponsor's decision to proceed with a higher (and more clinically relevant) dose. Only 3 subjects were exposed to dalbavancin in this study each receiving a single 70-mg dose infusion. All 1267 subjects received the drug intravenously.

Data Source

The primary sources for data analyses were the electronic datasets submitted by the sponsor as well as from Case Report Forms (CRFs). These sources included data on deaths, serious adverse events, other adverse events, and laboratory results.

Methodology

The CRFs were reviewed for evidence of adverse events and for unexplained patient withdrawal, to assess the safety of dalbavancin. Safety analyses were done in collaboration with the statistical reviewer, Dr. S. Bell. The *JMP* computer program was the main review tool employed by the primary medical reviewer that enabled independent analysis of data. Occasionally, *cross-graph* and *Web SDM* programs were used to cross-check specific pieces of information. For safety review purposes, any adverse events (AEs) or serious adverse events (SAEs) occurring in any subject who has received dalbavancin in the submitted application was evaluated. In each case, a determination was made about any relationship between the AE and dalbavancin. The occurrence of AEs in the comparator arm subjects was also evaluated for comparison with the dalbavancin arm.

Analyses done by the sponsor are presented in regular type and those by the medical reviewer in italics. Sponsor's tables are drawn in single lines; the reviewer's tables are drawn in double lines.

Methods of Analyses of Safety studies and Events

In this review, the sponsor's designation of studies as "VER001-" was replaced by "study" or "studies". Thus VER001-5 is simply referred to as study 5. In addition, "like studies" were pooled for analyses. Thus, the double-blinded Phase 3 studies (8 and 9) data were pooled for analyses. Similarly, the open-label phase 2 studies (4 and 5) and study 16 (Phase 3) were pooled for analyses. Phase 1 was analyzed separately. All data, including specific CRFs for outliers, were thoroughly scrutinized for evidence of treatment-emergent adverse events, their severity, duration, time to resolution, if reported, and causality.

Mortality Analysis

Study reports, sponsor's narratives (if provided), and CRFs describing patient deaths were reviewed. Events were examined to ascertain any evidence that relates death to drug exposure or to lack of drug efficacy. Patients were considered to have died from the initial infection if death occurred before the end of follow-up and:
1. the investigator indicated that the initial infection was the cause of death, and
2. the investigator's documented cause of death: a) directly correlated with an ongoing deteriorating infectious process and b) the observed clinical course of illness was consistent with persistence or progression of the original infection.

Discontinuations

All cases of discontinuations due to adverse events were examined for evidence of a relationship to study drug, or its lack of efficacy. In addition, discontinuation rates were compared among treatment groups and each group was examined to identify any specific subgroups of interest.

Adverse Events and Serious adverse events

An **event** included any side effect, injury, toxicity, sensitivity reaction, intercurrent illness, or sudden death. An **adverse event (AE**) included any adverse experience, whether or not it was considered drug-related, that occurred after the onset of study drug administration to a subject or a patient. A **serious adverse event (SAE)** was defined as any AE that was life-threatening or resulted in any of the following outcomes: death, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly, or birth defect. AEs that did not meet at least 1 criterion for an SAE were considered non-serious. However, an important medical event that did not meet the SAE criteria may have been considered an SAE if, based upon appropriate medical judgment, the event jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes mentioned.

Serious adverse events were reviewed, including examination of SAEs that might

represent lack of drug efficacy. SAE rates were determined by treatment group for specific subgroups of interest. Relationship of SAEs to study drug was ascertained and described as related, unrelated, unlikely related, possibly related, or probably related.

Laboratory values

Laboratory values were evaluated from the information in the database using the review tools previously mentioned to allow comparison between treatment groups and for specific subgroups of interest. Unusual situations (outliers) were identified and reviewed for evidence of a drug-effect relationship.

Extent of Exposure to Dalbavancin

Tables 1 and 2a show the overall number of subjects who participated in the studies and the various doses of dalbavancin received respectively. The three subjects prematurely terminated in study 3 were excluded from the sponsor's database. Nevertheless, their safety information was evaluated by the reviewer.
All 1267 subjects/patients received dalbavancin intravenously. The comparator group comprised 594 patients.

As shown in Table 1, 141 (11.1%), 81 (6.4%), and 1045 (82.5%) participants received dalbavancin in the Phase 1, Phase 2 and Phase 3 studies respectively. Sixty eight (5.4%) persons received doses < 1000 mg; 442 (35%) received a single dose of 1000 mg each, and 26 (2%) received a single dose > 1000 mg but < 1500 mg each (Table 2a). One subject in study 2 (Phase 1) received 1500 mg of dalbavancin as a single dose.

The dose of IV dalbavancin for the indication sought by the sponsor (cSSSI) is 1000 mg on day 1 followed by 500 mg on day 8. Of the 1267 subjects who received dalbavancin, 731 (57.7%) received this regimen. A total of 1201 (94.8%) subjects received doses ≥1000 mg in all the studies. The receipt of 1 dalbavancin dose of 1000 mg was defined as being equivalent to receiving 7 days of dalbavancin treatment. Similarly, receiving 2 dalbavancin doses (1000 mg on day 1 and 500 mg on day 8) was defined as being equivalent to receiving 14 days of dalbavancin treatment.

Table 1: Number of Subjects/Patients

Phase	Dalbavancin	Comparator (or placebo)	Total
1	141	19 **	160
2	81	55	136
3	1045	518	1563
Total	1267	Comparator = 573 Placebo = 19 (Total = 592)	1859

** Received placebo.
A total of 573 patients received comparator drugs while 19 subjects in Phase 1 received placebos.

Table 2a: Study Subjects Who Received Dalbavancin (and Doses) in All Studies									
Phase	**Study #**	**N**	**Received Dalbavancin**	**Highest Single mg Dose**	**Total Single Dose <1000 mg**	**Single 1000 mg only**	**Dose Range = 1001-1499 mg**	**D 1 = 1000mg D 8=500 mg**	**Total Dose ≥ 1000 mg**
1	**1**	23	17	490 (6)	17	-	-	-	-
1	**2**	52	39	1600 (2)	28	3	5	1 (1500 mg) 2 (1600 mg)	11
1	**3**	5	3	70 (3)	3	-	-	-	-
1	**10**	6	6	1000 (6)	-	6	-	-	6
1	**11**	19*	22	1000 (4)	18 (500mg)	4	-	-	4
1	**12**	27	27	1000 (27)	-	1		26	27
1	**13**	21	21	1000 (21)	-	21	-	-	21
1	**19**	9	9	1000 (9)	-	9	-	-	9
2	**4**	74 §	40	1170 (1)	2	3	1 (1170mg)	34	35
2	**5**	62**	41	1100 (20)	-	1	20 (1100 mg each)	20	41
3	**8**	553	367	1000 (273)	-	273	-	94	367
3	**9**	854	571	1000 (71)	-	71	-	500	571
3	**16**	156	107	1000 (50)	-	50	-	57	107
Total ⇒		**1864**	**1270 (1267)***	**N/A**	**68**	**442**	**26**	**734**	**1198* 1201**

D = Treatment Day; * Unique subjects (3 subjects dosed twice); N/A, Sum total not assessed
§ 75 randomized; 74 received Treatment: Dalbavancin = 33; Vancomycin = 34; Discontinued arm of daily dalbavancin = 7
** 59 completed study; 2 w/drawn (non-compliant); one w/drawn (took prohibited concomitant med)

Grouping of Studies for Analyses

For proper analyses and comparisons of study results, the studies in this submission have been
re-grouped in the following order:

1. Randomized, double-blind, multi-center studies: Protocols 8 and 9
2. Randomized , open-label, multi-center studies: Protocols 4, 5 and 16
3. Phase 1 Studies

By this grouping, Table 2b shows the number of subjects who received dalbavancin or placebo in Phase 1 studies as well as patients who received dalbavancin or comparators in Phases 2 and 3 studies.

Table 2b: All Subjects receiving Study Medications (Studies according to groups & subgroups)									
Phase 1 studies		**Studies 4, 5, and 16**				**Studies 8 and 9**			
Dalbavancin	**Placebo**	**Dalbavancin**		**Comparator**		**Dalbavancin**		**Comparator**	
N = 141	**N = 19**	**N = 188**		**N = 104**		**N = 938**		**N = 469**	
1 dose: <1000mg: n = 66 1000mg only: n = 44 2 doses: n = 31		**1 dose**	**2 doses**	**7 days**	**14 days**	**1 dose**	**2 doses**	**7 days**	**14 days**
		n = 75	**n =113**	**n =23**	**n = 81**	**n =344**	**n = 594**	**n = 153**	**n = 316**

Table 2c shows the number of patients from different studies in accordance with the grouping of the methodology outlined above.

Table 2c: Subjects Receiving Study Medications (Phases 2/3 only)					
Open-label controlled studies					
Phase	**Protocol**	**Dalbavancin**		**Comparator**	
		1 Dose	**2 Doses**	**7 Days**	**14 Days**
2	4	5	35	6	28
2	5	21	20	4	17
3	1 6	49	58	13	36
Subtotal ⇒		**75**	**113**	**23**	**81**
Double-Blind controlled studies					
Phase	**Protocol**	**Dalbavancin**		**Comparator**	
		1 Dose	**2 Doses**	**7 Days**	**14 Days**
3	8	273	94	134	52
3	9	71	500	19	264
Subtotal ⇒		**344**	**594**	**153**	**316**

Exposure to study drug by Disease Indication

As shown in table 2d, among the patients who received dalbavancin, 642 and 444 patients were treated for cSSSI and uSSSI respectively; 40 had catheter-related bloodstream infection (CRBSI). Among the 642 dalbavancin-treated patients with cSSSI, 96 (15.0%) received 1 dose, and 546 (85.0%) received 2 doses. A total of 322 patients with cSSSI received a comparator drug. Patients with uSSSI were enrolled in studies 8 and 16. Parenteral therapy was necessitated by disease severity and associated co-morbid conditions. Of the 444 dalbavancin-treated patients who had uSSSI, 318 (71.6%) received 1 dose, and 126 (28.4%) received 2 doses. A total of 217 patients with uSSSI received comparator treatment. Of the 40 dalbavancin patients who had CRBSI, 6 (15%) received 1 dose, and 34 (85%) received 2 doses. A total of 34 patients with CRBSI received a comparator drug.

Table 2d: Exposure to Study Drug by Disease Indication													
		cSSSI				**uSSSI**				**CRBSI**			
		D		**C**		**D**		**C**		**D**		**C**	
P	**S**	**1 dose**	**2 doses**	**7 days**	**14 days**	**1 dose**	**2 doses**	**7 days**	**14 days**	**1 dose**	**2 doses**	**7 days**	**14 days**
2	**4**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**6**	**34**	**6**	**28**
	5	**21**	**20**	**4**	**17**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
3	**8**	**0**	**0**	**0**	**0**	**273**	**94**	**134**	**52**	**0**	**0**	**0**	**0**
	9	**71**	**500**	**19**	**264**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	16	**4**	**26**	**2**	**16**	**45**	**32**	**11**	**20**	**0**	**0**	**0**	**0**
Subtotal		**96**	**546**	**25**	**297**	**318**	**126**	**145**	**72**	**6**	**34**	**6**	**28**
Total		**642**		**322**		**444**		**217**		**40**		**34**	
cSSSI = complicated skin and skin structure; **uSSSI** = *un*complicated skin and skin structure **CRBSI**= Catheter-related blood stream infection; **D** = Dalbavancin; **C**= Comparator; **P** = Phase; **S** = Study													

Demographic and Other Characteristics

Phases 2 and 3 Studies

Table 3a shows the demographic and other characteristics of the Phase 2/3 patients. Out of the 1699 patients treated in the Phase 2/3 integrated database, 1126 patients received dalbavancin; 573 patients received a comparator drug. The demographic characteristics considered included age, gender, and race/ethnicity. Number of patients in Study regions/locations, body mass index (BMI) and study indications were also described. The majority of Phase 2/3 patients were <65 years of age, male, and Caucasian. Of the disease indications, the majority of patients received treatment for cSSSI; CRBSI had the smallest proportions of patients in all Phase 2/3 studies. Studies were conducted in Europe and North America. Demographics were generally comparable for patients with cSSSI and uSSSI. A greater proportion of patients with CRBSI were ≥ 65 years of age than those patients treated for cSSSI or uSSSI. All patients with CRBSI participated in North America. The two treatment arms were similar in demographic characteristics.

Table 3a ISS 7: Demographic and Other Characteristics [Phases 2 and 3]

Characteristic	Dalbavancin			Comparator		
	1 Dose N=419	2 Doses N=707	Total N=1126	7 Days N=176	14 Days N=397	Total N=573
Age (Years)						
Mean (SD)	46.6	48.8	**48.0**	47.6(18.11)	48.2(16.95)	**48.0(17.30)**
Median	(17.08)	(16.7)	**(16.7)**	46.0	47.0	**47.0**
Range	45.0	47.0	**46.0**	18-85	18-92	**18-92**
	18-89	16-93	**16-93**			
Age distribution						
<65 years	346 (82.6)	573 (81.0)	**919 (81.6)**	143 (81.3)	325 (81.9)	**468 (81.7)**
≥65	73 (17.4)	134 (19.0)	**207 (18.4)**	33 (18.8)	72 (18.1)	**105 (18.3)**
Gender, N (%)						
Male	257 (61.3)	421(59.5)	**678 (60.2)**	**96**(54.5)	241(60.7)	**337(58.8)**
Female	162 (38.7)	286(40.5)	**448 (39.8)**	80 (45.5)	156(39.3)	**236 (41.2)**
Race/Ethnicity, N (%)						
Caucasian	303 (72.3)	498 (70.4)	**801 (71.1)**	143(81.3)	287(72.3)	**430 (75.0)**
Black	50 (11.9)	65 (9.2)	**115 (10.2)**	12 (6.8)	41 (10.3)	**53 (9.2)**
Asian	2 (0.5)	7 (1.0)	**9 (0.8)**	0	9 (2.3)	**9 (1.6)**
Hispanic/Latino	53 (12.6)	129 (18.2)	**182 (16.2)**	18 (10.2)	58 (14.6)	**76 (13.3)**
Other	11 (2.6)	8 (1.1)	**19 (1.7)**	3 (1.7)	2 (0.5)	**5 (0.9)**
BMI (kg/m^2)						
N	412	697	**1109**	174	394	**568**
Mean (SD)	29.3 (7.65)	30.9 (9.2)	**30.3 (8.7)**	29.0 (8.36)	30.2 (8.95)	**29.8 (8.78)**
Median	27.5	28.4	**28.1**	27.1	28.2	**27.9**
Minimum Maximum	17 61	15 98	**15 – 98**	14 69	16 91	**14 – 91**
Indication, N (%)						
cSSSI	96 (22.9)	546 (77.2)	**642 (57.0)**	25 (14.2)	297 (74.8)	**322 (56.2)**
uSSSI	318 (75.9)	126 (17.8)	**444 (39.4)**	145 (82.4)	72 (18.1)	**217 (37.9)**
CRBSI	5 (1.2)	35 (5.0)	**40 (3.6)**	6(3.4)	28 (7.1)	**34 (5.9**
Location, N (%)						
North America	292 (69.7)	618 (87.4)	**910 (80.8)**	110 (62.5)	345 (86.9)	**455 (79.4)**
Europe	127 (30.3)	89 (12.6)	**216 (19.2)**	66 (37.5)	52 (13.1	**118 (20.6)**

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days was based on actual exposure, not randomization to treatment.

Phase 1 Study

Demographic and other characteristics of the integrated Phase 1 study population are summarized in Table 3b. The 7 Phase 1 studies had 141 subjects who received dalbavancin and 19 subjects who received placebo.

The mean age was 42.5 years for subjects who received dalbavancin and 27.3 years for subjects who received placebo. The dalbavancin arm included special population subjects (i.e. subjects with renal or hepatic impairments). The majority of all subjects were <65 years, male, and Caucasian. Subjects who received 500 mg and > 1000 mg doses of dalbavancin had more males than females, and a greater racial/ethnic diversity.

Table 3b ISS 7: Demographic and Other Characteristics (Phases 1 Integrated database)

Characteristic	**Dalbavancin**				**Placebo**
	500 mg (N = 29)	**500 – 1000 mg(N = 78)**	**>1000 mg (N = 34)**	**Total N = 141)**	**(N = 19)**
Age (Years)					
Mean (SD)	31.5(8.04)	46.1(17.92)	43.4 (13.69)	**42.5 (16.32)**	**27.3 (7.18)**
Median	32.0	47.5	46.0	**42.0**	**25.0**
Range	18 - 52	20- 81	21- 67	**18 – 81**	**19 – 43**
Age distribution					
<65 years	29 (100)	63 (80.8)	32 (94.1)	**124 (87.9)**	**19(100)**
≥65	0	15 (19.2)	2 (5.9)	**17(12.1)**	**0**
Gender, N (%)					
Male	23 (79.3)	39(50.0)	22(64.7)	**84(59.6)**	**13 (68.4)**
Female	6 (20.7)	39(50.0)	12(35.3)	**57(40.4)**	**6 (31.6)**
Race/Ethnicity, N (%)					
Caucasian	25 (86.2)	51(65.4)	19 (55.9)	**95(67.4)**	**13 (68.4)**
Black	2 (6.9)	23(29.5)	6 (17.6)	**31(22.0)**	**4 (21.1)**
Asian	0	1(1.3)	1(2.9)	**2(1.4)**	**0**
Hispanic/Latino	1(3.4)	1(1.3)	7(20.6)	**9(6.4)**	**0**
Other	1(3.4)	2(2.6)	1(2.9)	**4(2.8**	**2 (10.5)**
BMI (kg/m^2)					
Mean (SD)	24.6 (2.25)	26.6 (4.61)	28.6(5.35)	**26.7(4.61)**	**24.3 (4.36)**
Median	24.5	26.6	29.8	**26.3**	**24.0**
Minimum Maximum	21 -31	17- 39	18- 39	**17 – 39**	**16 – 36**

MO's Comment: *The subjects exposed to dalbavancin and comparators in these studies appear balanced in demographic and other characteristics (age distributions, gender, race / ethnicity and subject BMIs) enough to allow a reasonable assessment of drug effect differences between subjects 1) across the study arms, 2) within study drug subgroups, and 3) between other subgroups of interest. Study 9 represents the pivotal study in this drug development program, being the double-blinded study which enrolled patients who had cSSSI, the disease for which the sponsor seeks indication. This study had the largest number of patients. Study 8, the other double- blinded study, allowed assessment of study drug effects in patients with uSSSI who were sick enough to require hospitalization. This study was conducted to be supportive of study 9 and had the next largest number of patients as shown in tables 2 (a, b, c and d) above.*

Overview of Adverse Events

An overview of AEs that occurred among Phase 2 and Phase 3 patients is shown in the two tables below. Table 3.5a is the overview of AEs in studies 8 and 9 and Table 3.5b, in studies 4, 5 and 16.
In studies 8 and 9, at least one AE occurred in 458 (48.8%) dalbavancin-treated patients compared to 243 (51.8 %) comparator-treated patients. The dalbavancin treatment-related AEs affected 194 (20.7 %) patients compared to 120 (25.6%) comparator-treated patients. Thus, the treatment-related events were slightly higher in the comparator arm. Most AEs were mild or moderate in intensity.

There were no treatment-related deaths. At least 1 SAE was reported in 64 (6.8%) dalbavancin-treated patients compared to 37 (7.9%) comparator-treated patients. Leukopenia, occurring in 2 (0.2%) dalbavancin-treated patients was the only treatment-related SAE in the dalbavancin arm, compared to 3(0.6 %) comparator-treated patients in whom SAEs were reported. The incidence of treatment-related SAEs was small and slightly higher in the comparator-treatment arm.

In studies 4, 5 and 16 (table 3.5b), at least one AE occurred in 127 (67.6%) dalbavancin-treated patients compared to 83 (79.8%) comparator-treated patients. The dalbavancin treatment-related AEs occurred in 54 (28.7%) patients compared to 37 (35.6%) comparator-treated patients. The treatment-related events were slightly higher also in the comparator arm. As in studies 8 and 9, most AEs were mild or moderate in intensity.

There were no treatment-related deaths in studies 4, 5 and 16. There was at least 1 SAE in 28 (14.9%) patients who received dalbavancin compared to 17 (16.3%) comparator-treated patients. There was no dalbavancin treatment-related SAE whereas 2 (1.9 %) comparator-treated patients had SAEs.

Table 3.5a (Modified Table ISS B1):	**Overview of Adverse Events among Studies 8 and 9 Patients**					
	Dalbavancin			**Comparator**		
Number (%) of patients:	**1 dose n =344**	**2 doses n =594**	**Total n=938**	**7 days n = 153**	**14 days n =316**	**Total n=469**
with at least one AE	122 (35.5)	336 (56.6)	458 (48.8)	57 (37.3)	186 (58.9)	243 (51.8)
with treatment-related AEs*	43 (12.5)	151 (25.4)	194 (20.7)	25 (16.3)	95 (30.1)	120 (25.6)
with at least one SAE	22 (6.4)	42 (7.1)	64 (6.8)	14 (9.2)	23 (7.3)	37 (7.9)
with at least one treatment-related SAE	0	1 (0.2)	1 (0.1)	1 (0.7)	2 (0.6)	3 (0.6)
with at least one AE leading to study drug discontinuation	29 (8.4)	6 (1.0)	35 (3.7)	6 (3.9)	6 (1.9)	12 (2.6)
with at least one AE leading to withdrawal from study	12 (3.5)	4 (0.7)	16 (1.7)	3 (2.0)	1 (0.3)	4 (0.9)
who died	3 (0.9)	2 (0.3)	5 (0.5)	1 (0.7)	4 (1.3)	5 (1.1)
who died due to treatment-related AE	0	0	0	0	0	0
Total number (%) of :						
treatment-related AEs	71 (24.5)	243 (27.3)	314 (26.6)	43 (26.4)	170 (28.8)	213 (28.2)
SAEs	26 (9.0)	45 (5.1)	71 (6.0)	17 (10.4)	31 (5.2)	48 (6.4)
treatment-related SAEs	0	1 (0.2)	1 (0.1)	1 (0.6)	2 (0.6)	3 (0.6)
Total number of AEs	290	889	1179	163	591	754

AE = adverse event; SAE = Serious adverse event; Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Treatment-related AEs are defined as those reported as possibly or probably related to study treatment or AEs for which the relationship was missing. For summarizations of number of patients, patients are only counted once; for number of AE summarizations, patients may be counted multiple times, according to the number of AEs experienced.

Table 3.5b (Modified Table ISS B2): Overview of Adverse Events among Studies 4, 5 and 16 Patients						
	Dalbavancin			**Comparator**		
Number (%) of patients:	**1 dose n =75**	**2 doses n =113**	**Total n=188**	**7 days n = 23**	**14 days n =81**	**Total n=104**
with at least one AE	47 (62.7)	80 (70.8)	127 (67.6)	16 (69.6)	67 (82.7)	83 (79.8)
with treatment-related AEs*	19 (25.3)	35 (31.0)	54 (28.7)	8 (34.8)	29 (35.8)	37 (35.6)
with at least one SAE	11 (14.7)	17 (15.0)	28 (14.9)	5 (21.7)	12 (14.8)	17 (16.3)
with at least one treatment-related SAE	0	0	0	1 (4.3)	1 (1.2)	2 (1.9)
with at least one AE leading to study drug discontinuation	4 (5.3)	0	4 (2.1)	7 (30.4)	3 (3.7)	10 (9.6)
with at least one AE leading to withdrawal from study	1 (1.3)	0	1 (0.5)	2 (8.7)	0	2 (1.9)
who died	3 (4.0)	1 (0.9)	4 (2.1)	1 (4.3)	1 (1.2)	2 (1.9)
who died due to treatment-related AE	0	0	0	0	0	0
Total number (%) of :						
treatment-related AEs	30 (19.0)	79 (16.5)	109 (17.1)	13 (33.3)	48 (16.8)	61 (18.8)
SAEs	17 (10.8)	26 (5.4)	43 (6.8)	5 (12.8)	13 (4.5)	18 (5.5)
treatment-related SAEs	0	0	0	1 (2.6)	1 (0.3)	2 (0.6)
Total number (%) of AEs	158	478	636	39	286	325

AE = adverse event; SAE = Serious adverse event; Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized Treatment. Treatment-related AEs are defined as those reported as possibly or probably related to study treatment or AEs for which the relationship was missing. For summarizations of number of patients, patients are only counted once; for number of AE summarizations, patients may be counted multiple times, according to experienced. Percentages of total number of treatment-related AEs and serious AEs are based on total number of AEs.

Overview of Adverse Events: Phase 1

Table 3.5c represents an overview of AEs for the Phase 1 integrated safety database (modified sponsor's ISS table 8).
Overall, at least 1 AE was reported in 105 (74.5%) subjects who received dalbavancin compared to 15 (78.9%) who received placebo. Treatment-related AEs were reported in 50 (35.5%) subjects who received dalbavancin compared to 11 (57.9%**)** who received placebo. Three (2.1%) subjects had AEs leading to treatment discontinuation.

There were no deaths or AEs that led to subject withdrawal from Phase 1 studies.
Two (1.4%) subjects who received dalbavancin had SAEs that were considered unrelated to study drug. The majority of AEs were mild in intensity.

Table 3.5c (Modified Sponsor's Table 8): Overview of Adverse Events (Phase 1 Subjects)

Characteristics	**Dalbavancin**				**Placebo**
Number (%) of subjects with:	**500 mg (N = 29)**	**500 – 1000 mg (N = 78)**	**>1000 mg (N = 34)**	**Total N = 141)**	**(N = 19)**
at least 1 AE	21 (72.4)	58 (74.4)	26 (76.5)	**105 (74.5)**	**15 (78.9)**
at least 1 treatment-related AE	13 (44.8)	24 (30.8)	13 (38.2)	**50 (35.5)**	**11 (57.9)**
at least 1 SAE	0	2 (2.6)	0	**2 (1.4)**	**0**
at least 1 treatment-related SAE	0	0	0	**0**	**0**
at least 1 AE→ D/cont. of med.	0	3 (3.8)	0	**3 (2.1)**	**0**
at least 1 AE→ w/drawal from study	0	0	0	0	**0**
Total number of AEs	62	147	67	276	**41**
Number (%) of :					
Treatment-related AEs	20 (32.3)	48 (32.7)	20 (29.9)	**88 (31.9)**	**22 (53.7)**
SAEs	0	3 (2.0)	0	**3 (1.1)**	**0**
Treatment-related SAEs	0	0	0	**0**	**0**
Deaths	0	0	0	**0**	**0**
Deaths due to treatment-related AE	0	0	0	**0**	**0**

→ D/cont. of med. = leading to discontinuation of study medication
→ w/drawal from study = leading to withdrawal from study

SERIOUS ADVERSE EVENTS

Serious Adverse Events (SAEs) presented in this review were defined as follows:

- Death;
- An immediately life-threatening adverse drug experience;
- Event necessitating inpatient hospitalization or prolongation of existing hospitalization;
- An event that is persistent or associated with significant disability/incapacity; or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, or be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.
Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.1.1 **Deaths**

Overview of Patient Deaths

Overall, and as shown in table 4a, 16 deaths were reported: 5 in study 4 (Phase 2), and 11 in studies 8, 9 and 16 (Phase 3). Of the 1085 subjects who received dalbavancin in all 4 studies, 9 (0.83%) died. By comparison, 7 (1.1%) of the 659 patients who received the comparator antibiotics in the same studies died. The demographic and other features for the 9 patients who died in the dalbavancin group were similar to the 7 in the comparator group. They had serious co-morbid conditions and were receiving many concomitant medications (see table 4b). Of the 9 deaths in the dalbavancin arm, 6/9 (66.7%) occurred among patients who each received a single dose, and 3/9 (33.3%) occurred in patients who each received two doses.

Table 4a: Number of Reported Deaths

	Number of Deaths					
Study number	**Study Drug**	**# of Pts (N)**	**Deaths n (%)**	**Comparator**	**# of Pts (N)**	**Deaths n (%)**
Study 4	Dalbavancin	40	3 (7.5)	Vancomycin	34	2 (5.9)
Study 8	Dalbavancin	367	3 (0.82)	Cefazolin	186	3 (1.6)
Study -9	Dalbavancin	571	2 (0.35)	Linezolid	283	2 (0.7)
Study 16	Dalbavancin	107	1 (0.93)	Vancomycin	156	0
Total →	**Dalbavancin**	**1085**	**9 (0.83)**	**Comparator**	**659**	**7 (1.1)**

Pts. = Patients

Table 4b:
Deaths in Patients Who Received Dalbavancin, Their Co-morbidities and Concomitant medications

PTID, age, and race	# of Doses	Day from initial Dose	Suspected Cause of death	Co-morbid Conditions	Concomitant medications
04-002-218 75 y/o WF	2	22	Progression of underlying medical conditions	Diabetes mellitus, rheumatoid arthritis, hyponatremia, urinary tract infection, renal failure, metabolic acidosis, dehydration, anemia	protonix, KCl morphine, K-Phos, Aztreonam (UTI) Levofloxacin (pneumonia) Restoril, laxis, MgSO4, Voltaren, Solumedrol, etc
04-036-24 55 y/o BM	1	21	Possible perforated Small bowel	Ileus, COPD, Seizures, Diabetes mellitus, hypertension Parkinson's, Hyperlipidemia, Coronary Artery Disease UTI, Pneumonia hypoglycemia and hypotension	Accuzyme, Lasix, Dilantin, Humulin, norvasc, lopressor, Trihexphenidyl, Zosyn, amikacin, Aztreonam, Tobra, etc..
04-036-508 68 y/o BF	1	17	Two spontaneous Post- Tracheostomy procedure site bleeds (On Days 7 and 17)	COPD, GERD , hypertension, and anemia, diabetes mellitus bilateral pleural effusion, respiratory failure, ventilator-dependence	Combivent, humulin, laxis famotidine, enoxaparin metoprolol, Diltiazem, KCl dopamine (↓BP), cefepime aztreonam, flagyl, Vancomycin, zyvox (UTI)
08-020-002 67 y/o BF	1	1	Gram-negative bacteremia ⇓ Shock → Death	-Deep Vein Thrombosis -Acute refractory hypertension Transient Ischaemic Attacks. Mental Status Changes Hypothyroidism	Mirtazapine, levothyroxine Fexofenadine, Lansoprazole Fluoxetine, Sertraline, Olanzapine, Glipizide Metoprolol, Acetylcysteine Lasix, Zithromax, Rocephin, Pip-Tazo
08-033-019 84 y/o WM	2	21 (6 days post last dose)	- Congestive heart failure (CHF) -Atrial fibrillation -Bradycardia	-Diabetes mellitus -Pacemaker placement -Peripheral vascular disease -Bilateral lower extremity edema	Bumetanide, KCL, finasteride, Foltrin, Metoprolol, Warfarin Epinephrine, atropine, Levofloxacin
08-045-001 82 y/o WM	1	23	-Severe acute renal failure -Atrial Fibrillation -Respiratory distress	Occluded graft of previous coronary bypass surgery. -Procedures: abdominal and lower extremity angiogram, -cardiac catheterization - GI bleeding --Contrast –induced nephropathy	Propoxyphene, nifedipine, Albuterol, ipratropium, Enoxaparin, Flagyl, morphine, Ranitidine, metporolol, Pip/tazo,Nitroglycerin, KCL clopidogrel, Midazolam, lopazepam, lasix, calcium Dopamine, Pantoprazole, etc
09-037-011 59 y/o BF	1	4	Congestive heart failure	Diabetes mellitus, renal insufficiency (mild) anemia, leukocytosis	Insulin, KCL, Thioridazine, Doxepin, diphenoxylate, Albuterol, ipratropium, Atropine, Levofloxacin, ceftriaxone, Flagyl
09-250-017 55 y/o WM	2	10	Severe myocardial Infarction	Coronary artherosclerosis	aspirin, atenolol, simvastatin perindopril, clopidogrel, enoxaparin, glyceryl trinitrate
16-036-004 74 y/o WF	1	10	Worsening CHF	CHF; atrial fibrillation; Hypertension; COPD; Pulmonary hypertension	Pantoprazole, percocet, taplisol, aspirin, Lasix, atenelol, ipratroium, digoxin, etc, etc..

CHF= congestive heart Failure; COPD= chronic obstructive pulmonary Disease; KCL= Potassium Chloride; MgSO4= magnesium Sulphate; GERD= gastroesophageal reflux disease; UTI= urinary tract infection; WM= white male; BM= black male; WF=white female; BF= black female; PTID = Patient Identification Number

Deaths by Study Subgroups

Table 4c is a summary table of patient deaths according to the individual study in both dalbavancin-treated and comparator-treated patients. The occurrence of deaths within the study subgroups by the number of doses (dalbavancin) or duration of antibiotics received (Days, in the comparator-treated patients) is also shown.

Of the 16 subjects who died, 5 (31%) died in study 4; 6 (38%) in study 8; 4 (25%) in study 9; and 1(6.3%) in study 16. Within the subgroups, 6/398 (1.5%) subjects who received a single dose of dalbavancin, 3/687 (0.4%) who received 2 doses of dalbavancin; 4/172 (2.3%) who received 7 days and 3/380 (0.8%) who received 14 days of the comparator treatments died. Thus, in this subgroup analysis, the patients who received 7 days of the comparator treatment had the highest rate (2.3 %) of deaths.

Table 4c: Summary of Deaths by Studies and Subgroups

	Dalbavancin		**Comparator**		**Total**
Study	**1 dose n = 398**	**2 doses n = 687**	**7 days n = 172**	**14 days n = 380**	
4	2	1	2	0	5
8	2	1	1	2	6
9	1	1	1	1	4
16	1	0	0	0	1
Subgroup Total	6 (1.5%)	3 (0.4 %)	4 (2.3 %)	3 (0.8%)	16
Group Total	9 (0.8 %)		7 (1.2%)		

Demographic and Clinical Characteristics of Patients who Died

Tables 4d-4g outline the demographic and treatment characteristics of the individual subjects that died in the studies. The investigator's assessments of the temporal sequence of patient deaths relative to the study drug administration are included.

In the dalbavancin arm, patients ranged in age from 55-84 years (median, 68years). Five were Caucasians, and 4 Blacks; 4 males and 5 females. The final cause of death was generally cardio-respiratory failure. For each patient, the underlying illnesses and suspected primary cause of death were usually multiple and severe, including complications of diabetes mellitus, refractory hypertension, and acute hemorrhagic events (see table 4).
In the comparator arm, the patient's age ranged from 47-82 years (median, 67 years). Four patients were Caucasian, 2 Black and one Hispanic. Aside from one patient (04-008-489) who had gastric cancer, the final causes of death, the underlying illnesses and the suspected primary causes of death for dalbavancin-treated patients were similar to the comparator-treated group.

Table 4d: Table of Patients who died in study 4 (Phase 2)

PID / Drug received	Age, Race, Gender	№ of doses/ or Duration of ℞x	Day into treatment patient died	Final cause Of Death	Suspected Cause of death	Co-morbid conditions (Description)	Temporal Sequence of drug to death	Investigator's Assessment : relationship to study drug
04-002-218 Dalbavancin	75 y/o WF	2 / = 14 days	Day 22	Respiratory Failure	Progression of other medical conditions	Rheumatoid arthritis, hyponatremia, diabetes mellitus, urinary tract infection, metabolic acidosis, dehydration, anemia	Possibly	Considered unrelated
04-036-224 Dalbavancin	55 y/o BM	1 / =7 days	Day 21	Cardiopulmonary Failure	Possible perforated Small bowel	Ileus	Possibly	Considered unrelated
04-036-508 Dalbavancin	68 y/o BF	1 / =7 days	Day 17	Cardio-respiratory Arrest	Two Post-Tracheostomy spontaneous procedure site bleeding (On Days 7 and 17)	Respiratory failure, ventilator-dependence, hypertension, and anemia.	Possibly	Considered unrelated
Vancomycin 04-008-489	65 y/o WF	8 days	Day 9	Cerebrovascular Accident (CVA)	CVA	Thrombocytopenia Anemia	Possibly	Considered unrelated
04-008-489 Vancomycin	64 y/o HF	7 days	Day 12	Gastric Cancer	Gastric Cancer	Not reported	Possibly	Considered unrelated

PID = Patient Identification Number

Table 4e: Deaths in study 8 (Phase 3)

PID / Drug received	Age, Race, Gender	№ of doses/ or Duration of Rx	Day into treatment patient died	Final cause Of Death	Suspected Cause of death	Co-morbid conditions (Description)	Temporal Sequence	Investigator's Assessment : relationship to study drug
0802002/ Dalbavancin	67 y/o BF	1	Day 2	Cardiogenic shock	Gram-negative bacteremia	-Deep Vein Thrombosis -Acute refractory hypertension Transient Ischemic Attacks. Mental Status Changes	Possibly	Considered unrelated
08033019/ Dalbavancin	84 y/o WM	2	Day 21 6 days after the last dose	Cardiac Arrest	- Congestive heart failure -Atrial fibrillation -Bradycardia	-Diabetes mellitus -Pacemaker placement -Peripheral vascular disease - Edema: lower limbs	Possibly	Considered unrelated
08045001/ Dalbavancin	82 y/o WM	1	Day 23	Cardio-pulmonary Failure	-Severe acute renal failure -Atrial Fibrillation -Respiratory distress	-Occluded graft of past coronary bypass surgery. -Procedures: abdominal & lower limb angiogram, -cardiac catheterization - GI bleeding -Contrast nephropathy	Possibly	Considered unrelated
08002003 Cefazolin	76 y/o WM	15 days Died 6 days post last dose	Day 21 One week post COPD exacerbation	COPD (exacerbation)	COPD exacerbation Cor pulmonale	-Diabetes mellitus -Hypertension - Atrial fibrillation -Peripheral edema -Steroid Dependency	Possibly	Considered Unlikely related
08023009 Cefazolin	72 y/o WF	15 days	Day 55	-Severe acute coronary syndrome -CCF	Same	-Diabetes mellitus -Hypertension, CVA - Venous insufficiecy	Possibly	Considered Unrelated
08050008 Cefazolin	67 y/o WF	7 days	Day 12	Cardiac Arrest	CHF; Atrial fibrillation	-Obesity -Proteinuria -Bradycardia	Possibly	Considered unrelated

PID = Patient Identification Number

Table 4f: Deaths in study 9 (Phase 3)

PID / Drug received	Age, Race, Gender	№ of doses/ or Duration of treatment	Day into treatment patient died	Final cause Of Death	Suspected Cause of death	Co-morbid conditions (Description)	Temporal Sequence of drug to death	Investigator's Assessment : relationship to study drug
09037011 Dalbavancin	59 y/o BF	1	Day 4	Cardiac asystole	Congestive heart failure	Diabetes mellitus, renal insufficiency(mild) Anemia, leukocytosis	Possibly	Considered unrelated
09250017 Dalbavancin	55 y/o WM	2	Day 10	Severe repeat myocardial infarction on Day 9	Severe myocardial infarction	Coronary arteriosclerosis	Possibly	Considered Unlikely related
09024033 Linezolid	47 y/o BM	8 days	Day 12	CVA	CVA complications, pericardial effusion, thoracotomy, pericardial stripping	Diabetes mellitus; Hypertension; CHF; Atrial fibrillation; obesity; liver disease; COPD -coronary artery disease	Possibly	Considered unrelated
09250010 Linezolid	82 y/o WF	15 days	Day 48	Pulmonary edema	Pulmonary edema; (L) ventricular failure	Peripheral vascular disease; H/o femoro-popliteal bypass; COPD; ® foot osteomyelitis	Possibly	Considered unrelated

PID = Patient Identification Number

Table 4g: Deaths in study 16 (Phase 3)

		Age, Race, Gender	№ of doses/ or Duration of Rx	Day into treatment patient died	Final cause Of Death	Cause of death	Co-morbid conditions (Description)	Temporal Sequence of drug to death	Investigator's Assessment : relationship to study drug
16036004		74 y/o WF	1 / =7 days	Day 10	Worsening CHF	Worsening CHF	Hospital D/C on Day 6; Readmitted on Day 7 CHF; atrial fibrillation; Hypertension; COPD; Pulmonary hypertension;	Possibly	Considered unrelated

PID = Patient Identification Number

Reasons for Deaths (Studies 8 and 9 patients)

The reasons for deaths (by system organ) among studies 8 and 9 patients are outlined in table 4h. One subject in the dalbavancin group died of severe sepsis, another from severe acute renal failure. Six deaths (3 in the dalbavancin group, 3 in the comparator group) resulted from cardiovascular complications.

Table 4h Summary of Reasons for Deaths by system organ (Studies 8 and 9)

Body Organ System	Dalbavancin		Comparator	
	N = 344	N= 594	N = 153	N=316
	1 dose	2 doses	7 days	14 days
	n (%)	n (%)	n (%)	n (%)
Number of deaths	3 (0.9)	2 (0.3)	2 (1.3)	3 (0.9)
BODY				
Sepsis	1 (0.3)			
CARDIOVASCULAR				
Cardiac arrest NEC			1 (0.7)	
Congestive Heart failure	1 (0.3)	1 (0.2)		1 (0.3)
Myocardial infarction		1 (0.2)		
Cardiovascular Accident			1 (0.7)	
RESPIRATORY				
Pulmonary Edema				1 (0.3)
COPD (Exacerbated)				1 (0.3)
RENAL				
Severe Acute Renal Failure	1 (0.3)			
Total	Dalbavancin group =5 (0.5)		Comparator group = 5 (1.1)	

Deaths in Patients in Studies 4 and 16

There were no deaths reported or recorded in study 5. Of the deaths reported in studies 4 and 16 (table 4i), 4/147 (2.7 %) occurred in the dalbavancin arm while 2/83 (2.4%) occurred in the comparator arm. The causes of death were also similar. The sponsor concluded that these deaths were not related to administration of dalbavancin. [The reviewer's comments on these deaths are on page 29].

Table 4i: Summary of Reasons for Death by System Organ (Studies 4, and 16)

Body Organ System	Dalbavancin		Comparator	
	N = 54	N = 93	N = 19	N = 64
	1 dose	2 doses	7 days	14 days
	n (%)	n (%)	n (%)	n (%)
Number of deaths	3 (4)	1 (1.1)	2 (10.5)	0 (-)
BODY				
Multiple organ failure		1 (1.1)		
CARDIOVASCULAR				
Congestive Heart failure (worsening)	1 (1.9)			
Cardiovascular Accident			1 (5.3)	
DIGESTIVE				
Gastrointestinal Perforation & bleeding	1 (1.9)			
Gastric cancer			1 (5.3)	
RESPIRATORY				
Post Tracheostomy Bleeding	1(1.9)			
Total	Dalbavancin group = 4 (2.7%)		Comparator group = 2 (2.4 %)	

MO's Comment: *From the foregoing (Table 4b; tables 4d-i), overall, in controlled clinical trial of SSSI, patient deaths were balanced in dalbavancin-treated and comparator-treated groups. The patients who died were generally severely il, had multiple co-morbid conditions, and probably could not be salvaged even by successful treatment of their SSSI and other infections. In addition, they were on multiple concomitant medications (table 4b).In the sponsor's assessment, these deaths were unrelated or unlikely related to dalbavancin administration. In reviewing each case of death, there was none in which the direct contribution of dalbavancin to the patient's death was apparent. Therefore, the medical reviewer agrees with the lack of direct evidence for a relationship between receipt of dalbavancin and mortality in these patients.*

Deaths Among Subjects in Phase 1 Studies.

There were no reported deaths among subjects who participated in Phase 1 clinical studies who received dalbavancin.

7.1.2 Other Serious Adverse Events

Serious adverse events

Table 5a shows the dalbavancin-treated and comparator treated subjects who had at least one occurrence of an SAE. Among the 938 subjects who received dalbavancin in studies 8 and 9, 64 (6.8%) subjects had at least one SAE. Among the 469 subjects who received the comparator treatment 37 (7.9%) developed at least one SAE. Among the 344 subjects who received a single dose of dalbavancin, 22 (6.4%) had at least one SAE compared to 42/594 (7.1%) who received 2 doses of dalbavancin, 14/153 (9.2%) who received 7 days of the comparator or 23/316 (7.3) who received 14 days of the comparator treatment. The frequencies of these SAEs are similar across study arms. With respect to the subgroups, the rate of SAEs in patients who received 1 dose of dalbavancin is slightly less than among the patient who received 7 days. Otherwise, the frequencies of SAEs in other subgroups are similar.
Treatment-related SAEs are also comparable across study arms.

Table 5a: Overall Frequencies of Serious Adverse Events among Studies 8 and 9 Patients

	Dalbavancin			Comparator		
Number (%) of patients:	**1 dose n =344**	**2 doses n =594**	**Total n=938**	**7 days n = 153**	**14 days n =316**	**Total n=469**
with at least one SAE	22 (6.4)	42 (7.1)	64 (6.8)	14 (9.2)	23 (7.3)	37 (7.9)
with at least one treatment-related SAE	0	1 (0.2)	1 (0.1)	1 (0.7)	2 (0.6)	3 (0.6)
Total number (%) of :						
SAEs	26 (9.0)	45 (5.1)	71 (6.0)	17 (10.4)	31 (5.2)	48 (6.4)
treatment-related SAEs	0	1 (0.2)	1 (0.1)	1 (0.6)	2 (0.6)	3 (0.6)

Frequencies of SAEs in Subjects in Studies 8 and 9

Table 5b shows the number of patients who had SAEs in decreasing order of frequencies in studies 8 and 9. Table 5c and Table 5d show SAEs that occurred in study patients (studies 8 and 9) by system organ. By system organs, among the 938 study subjects who received dalbavancin and the 469 who received the comparator antibiotics, infections and infestations were the most common SAEs, affecting subjects at a frequency over 4 times as high as cardiac SAEs, the second highest category.

The only SAE that occurred at ≥ 1% was cellulitis, reported by 11/938 (1.2 %) patients who received dalbavancin and by 4/469 (0.9%) patients who were comparator- treated. Within the subgroups, 4/344 (1.2%) patients who received 1 dose of dalbavancin had a slightly lower rate than 3/153 (2.0%) patients who received 7 days of the comparator treatment. Seven of 594 (1.2%) patients who received 2 doses of dalbavancin had SAEs compared to 1/316 (0.3%) comparator-treated patients. The reports of cellulitis were in subjects requiring re-hospitalization following a recurrence of cellulitis at the same or a different site after previous treatment. In some cases, persistence of cellulitis necessitated prolongation of hospitalization. There was no apparent dose-related pattern for any SAE. The less frequent SAEs that occurred in studies 8 and 9 are in the ISS tables in the appendix section.

MO's Comment: *The incidence of SAEs in the dalbavancin and the comparator arms were similar. No dose-related SAE was apparent. Although the numbers was small, the frequency of treatment-related SAEs was higher in the comparator arm than in the dalbavancin arm. However, the difference is neither statistically nor clinically significant.*

Table 5b (Modified Sponsor's Table B. 7): Serious Adverse Events by Decreasing Frequency in Studies 8 and 9

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
Number (%) of patients with at least one AE	22 (6.4)	42 (7.1)	64 (6.8)	14 (9.2)	23 (7.3)	37 (7.9)
CELLULITIS	4 (1.2)	7 (1.2)	11 (1.2)	3 (2.0)	1 (0.3)	4 (0.9)
ABSCESS LIMB	1 (0.3)	2 (0.3)	3 (0.3)	0	0	0
OSTEOMYELITIS NOS	0	2 (0.3)	2 (0.2)	1 (0.7)	2 (0.6)	3 (0.6)
ACCIDENTAL OVERDOSE	1 (0.3)	1 (0.2)	2 (0.2)	0	1 (0.3)	1 (0.2)
DEEP VEIN THROMBOSIS	0	2 (0.3)	2 (0.2)	0	1 (0.3)	1 (0.2)
PERIANAL ABSCESS	0	2 (0.3)	2 (0.2)	0	1 (0.3)	1 (0.2)
ASTHMA NOS	0	2 (0.3)	2 (0.2)	0	0	0
IMPAIRED HEALING	0	2 (0.3)	2 (0.2)	0	0	0
INFECTION NOS	2 (0.6)	0	2 (0.2)	0	0	0
LEUKOPENIA NOS	0	2 (0.3)	2 (0.2)	0	0	0
PERIPHERAL ISCHAEMIA	1 (0.3)	1 (0.2)	2 (0.2)	0	0	0
SKIN AND SUBCUTANEOUS TISSUE ABSCESS NOS	2 (0.6)	0	2 (0.2)	0	0	0
RENAL FAILURE ACUTE	1 (0.3)	0	1 (0.1)	0	3 (0.9)	3 (0.6)
PNEUMONIA NOS	0	1 (0.2)	1 (0.1)	1 (0.7)	1 (0.3)	2 (0.4)
CARDIAC ARREST	0	1 (0.2)	1 (0.1)	1 (0.7)	0	1 (0.2)
CARDIAC FAILURE CONGESTIVE	0	1 (0.2)	1 (0.1)	1 (0.7)	0	1 (0.2)
CONFUSIONAL STATE	1 (0.3)	0	1 (0.1)	0	1 (0.3)	1 (0.2)

Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Table 5c: Number (%) of Patients with SAEs in Studies 8 and 9 by organ systems.						
	Dalbavancin			Comparator		
Preferred term	1 dose N=344	2 doses N=594	Total N=938	7 days N=153	14 days N=316	Total N=469
Infections and Infestations						
Cellulitis	4 (1.2)	7 (1.2)	**11(1.2)**	3 (2.0)	1 (0.3)	**4 (0.9)**
Abscess limb	1 (0.3)	2 (0.3)	**3 (0.3)**	0	0	**0**
Osteomyelitis	0	2 (0.3)	**2 (0.2)**	1(0.7)	2 (0.6)	**3 (0.6)**
Pneumonia NOS	0	1 (0.2)	**1 (0.1)**	1(0.7)	1 (0.3)	**2 (0.4)**
Perianal abscess	0	2 (0.3)	**2 (0.2)**	0	1 (0.3)	**1(0.1)**
Necrotising Fasciitis NOS	1 (0.3)	0	**1 (0.1)**	0	1 (0.3)	**1(0.1)**
Infection NOS	2 (0.6)	0	**2 (0.2)**	0	0	0
Skin & subcutaneous tissue abscess NOS	0	2 (0.3)	**2 (0.2)**	0	0	0
Abscess NOS	0	0	0	1(0.7)	0	**1 (0.1)**
Arthritis Infective NOS	0	0	0	1(0.7)	0	**1 (0.1)**
Gastroenteritis NOS	0	0	0	0	1 (0.3)	**1 (0.1)**
Furuncle	0	1 (0.2)	**1 (0.1)**	0	0	0
Abdominal wall infection	0	0	0	1(0.7)	0	**1 (0.1)**
Staphylococcal Infection	0	0	0	1(0.7)	0	**1 (0.1)**
Staphylococcal sepsis	0	0	0	1(0.7)	0	**1 (0.1)**
Vulval abcess	0	0	0	1(0.7)	0	**1 (0.1)**
Urinary Tract Infection NOS	0	0	0	1(0.7)	0	**1 (0.1)**
Wound Infection	0	1 (0.2)	**1 (0.1)**	0	0	0
Viral Infection NOS	0	1 (0.2)	**1 (0.1)**	0	0	0
Cardiac disorders						
Cardiac Arrest	0	1 (0.2)	**1 (0.1)**	0	1 (0.3)	**1 (0.1)**
Congestive Heart failure	0	1 (0.2)	**1 (0.1)**	0	1 (0.3)	**1 (0.1)**
Pericardial Effusion	0	0	0	0	1 (0.3)	**1 (0.1)**
Myocardial Infarction	0	1 (0.2)	**1 (0.1)**	0	0	0
Cardiopulmonary Failure	1 (0.3)	0	**1 (0.1)**	0	0	0
Cardiogenic Shock	1 (0.3)	0	**1 (0.1)**	0	0	0
Atrial fibrillation	1 (0.3)	0	**1 (0.1)**	0	0	0
Anginal Pectoris	0	1 (0.2)	**1 (0.1)**	0	0	0
Acute Coronal Syndrome	0	0	0	0	1 (0.3)	**1 (0.1)**
Respiratory/thoracic/mediastinal						
COPD (Exacerbated)	0	0	0	1 (0.7)	1 (0.3)	**2 (0.4)**
Asthma NOS	0	2 (0.3)	**2 (0.2)**	0	0	0
Bronchitis NOS	0	1 (0.2)	**1 (0.1)**	0	0	0
Pulmonary edema NOS	0	0	0	0	1 (0.3)	**1 (0.1)**
Dyspnea	0	1 (0.2)	**1 (0.1)**	0	0	0
Injury/ poisoning/procedural						
Accidental Overdose	1 (0.3)	1 (0.2)	**2 (0.2)**	0	1 (0.3)	**1 (0.1)**
Medication Error	1 (0.3)	0	**1 (0.1)**	0	0	0
Therapeutic Agent Poisoning	0	1 (0.2)	**1 (0.1)**	0	0	0
Hip Fracture	0	1 (0.2)	**1 (0.1)**	0	0	0
Fall	0	1 (0.2)	**1 (0.1)**	0	0	0
Vascular disorders* (all 6 in study 9)						
Deep Vein Thrombosis	0	2 (0.3)	**2 (0.2)**	0	1 (0.3)	**1(0.1)**
Peripheral Ischaemia	1 (0.3)	1 (0.2)	**2 (0.2)**	0	0	**0**
Peripheral occlusive disease	0	1 (0.2)	**1 (0.1)**	0	0	**0**

COPD: chronic obstructive pulmonary airway disease

Table 5d: Number (%) of Patients with SAEs in Studies 8 and 9 by organ systems (Continued)						
Preferred term	**Dalbavancin**			**Comparator**		
	1 dose N=344	**2 doses N=594**	**Total N=938**	**7 days N=153**	**14 days N=316**	**Total N=469**
Psychiatric disorders						
Confusion State	1 (0.3)	0	**1 (0.1)**	0	1 (0.3)	**1 (0.1)**
Major Depressive Disorder NOS	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Obsessive –Compulsive Disorder	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Renal and urinary disorders						
Renal Failure Acute	1 (0.3)	0	**1 (0.1)**	0	**3 (1)**	**3 (0.6)**
Renal Failure NOS	1 (0.3)	0	**1 (0.1)**	0	0	**0**
Nephrolithiasis	1 (0.3)	0	**1 (0.1)**	0	0	**0**
Gastrointestinal disorders						
Abdominal Pain NOS	0	0	**0**	2 (1.3)	1 (0.3)	**3 (0.6)**
Gastrointestinal hemorrhage	1 (0.3)	0	**1 (0.1)**	0	0	**0**
Pancreatitis Acute	0	0	**0**	1(0.7)	0	**1 (0.1)**
Blood and lymphatic system disorders						
Pancytopenia	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Leukopenia NOS	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Thrombocytopenia	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Leukocytosis	0	1 (0.2)	**1 (0.1)**	0	0	**0**
Neoplasms/benign/ malignant/unspecified						
Hepatic Neoplasm	0	1 (0.2)	**1 (0.1)**	0	0	**0**
Breast Cancer NOS	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Non-Hopkins Lymphoma	0	1 (0.2)	**1 (0.1)**	0	0	**0**
Metastatic Neoplasm NOS; 1^0 site unknown	0	1 (0.2)	**1 (0.1)**	0	1 (0.3)	**1 (0.1)**
General disorders/infusion site conditions						
Cardiac Death	1 (0.3)	0	**1 (0.1)**	0	0	**0**
Chest Pain	1 (0.3)	0	**1 (0.1)**	0	0	**0**
Impaired Healing	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Nervous system disorders						
Cerebrovascular Accident	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Syncope	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Sleep Apnea Syndrome	1 (0.3)	0	**1 (0.1)**	0	0	**0**
Myoclonus	0	1 (0.2)	**1 (0.1)**	0	0	**0**
Musculoskeletal/connective tissue disorder						
Pain in Extremity	0	1 (0.2)	**1 (0.1)**	0	0	**0**
Arthralgia	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Metabolism and nutrition disorders						
Diabetes Mellitus Inadequate Control	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Hypoglycemia NOS	0	1 (0.2)	**1 (0.1)**	0	0	**0**
Hepatobiliary disorders						
Cholecystitis NOS	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Eye disorders						
Diplopia	0	0	**0**	0	1 (0.3)	**1 (0.1)**
Skin and subcutaneous tissue disorders						
Rash NOS	0	1 (0.2)	**1 (0.1)**	0	0	**0**
Investigations						
Renal Function Tests NOS Abnormal	1 (0.3)	0	**1 (0.1)**	0	0	**0**

SAEs among Studies 4, 5 and 16 Patients

By system organ class, infections and infestations constitute the most frequent SAEs also among patients in studies 4, 5 and 16. Table 5e is a comparative display of the overall number of patients who experienced SAEs while receiving either dalbavancin or the comparator. Accordingly, of the 188 patients who received dalbavancin in these studies, 28 (14.9%) had at least one SAE, slightly less in rate than the 18/104 (17.3%) patients who were comparator-treated. Within the subgroups, 11/75 (14.7%) who received 1 dose of dalbavancin had at least one SAE compared to 5/23 (21.7%) who received 7 days of the comparator treatment. Among the patients who received 2 doses of dalbavancin, 17/113 (15.0%) had at least one SAE, similar to 12/81 (14.8%) who received 14 days of the comparator treatment.
As also shown in table 5e, the percentage of total number of SAE instances were slightly higher in the dalbavancin-treated arm than in the comparator treated group (6.8% vs 5.5%). However, there were no treatment-related SAEs among the dalbavancin–treated patients.

Table 5e:Overall Number (%) of Serious Adverse Events among Studies 4, 5 and 16 Patients

	Dalbavancin			Comparator		
Number (%) of patients:	**1 dose n =75**	**2 doses n =113**	**Total n=188**	**7 days n = 23**	**14 days n =81**	**Total n=104**
with at least one SAE	11(14.7)	17 (15.0)	28 (14.9)	5 (21.7)	12 (14.8)	17 (16.3)
with at least one treatment-related SAE	0	0	0	1 (4.3)	1 (1.2)	2 (1.9)
Total number (%) of :						
SAEs	17 (10.8)	26 (5.4)	43 (6.8)	5 (12.8)	13 (4.5)	18 (5.5)
treatment-related SAEs	0	0	0	1 (2.6)	1 (0.3)	1 (0.6)
Total number (%) of AEs	158	478	636	39	286	325

MO's Comment: *Overall, per table 5e, the rates of SAEs appeared slightly higher in the comparator group compared to dalbavancin-treated patients. However, treatment-related SAEs were absent in the dalbavancin-treated patients, compared to 2/104 (1.9%) of comparator-treated subjects.*

The Frequencies of Other SAEs

Table 5f lists the SAEs that occurred in studies 4, 5 and 16 in decreasing order of frequency. For the tables of less frequent SAEs recorded in order of frequency, refer to the ISS tables in the appendix section (appendix 5). Tables 5g and 5h summarize the SAEs in dalbavancin-treated and comparator-treated subjects by preferred terms.
The most frequently occurring SAE was cellulitis, reported by 2 /75 (2.7%) patients who received 1 dose of dalbavancin, none in the subgroup who received 7 days of the comparator, none in patients who received 2 doses of dalbavancin, and 1/81 (1.2%) in patients who received 14 days of the comparator treatment. Other than cellulitis, no SAE occurred with a frequency of >2 % in any treatment arm.

Table 5f Sponsor's Table of Serious Adverse Events in Decreasing Order of Frequency in Studies 4, 5 and 16

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
Number (%) of patients with at least one AE	11 (14.7)	17 (15.0)	28 (14.9)	5 (21.7)	12 (14.8)	17 (16.3)
CELLULITIS	2 (2.7)	0	2 (1.1)	0	1 (1.2)	1 (1.0)
PYREXIA	1 (1.3)	1 (0.9)	2 (1.1)	0	1 (1.2)	1 (1.0)
CARDIAC FAILURE CONGESTIVE	1 (1.3)	1 (0.9)	2 (1.1)	0	0	0
CARDIO-RESPIRATORY ARREST	0	2 (1.8)	2 (1.1)	0	0	0
FEBRILE NEUTROPENIA	0	2 (1.8)	2 (1.1)	0	0	0
RESPIRATORY FAILURE (EXCL NEONATAL)	0	2 (1.8)	2 (1.1)	0	0	0
ATRIAL FIBRILLATION	0	1 (0.9)	1 (0.5)	0	1 (1.2)	1 (1.0)
BACTERAEMIA	0	1 (0.9)	1 (0.5)	0	1 (1.2)	1 (1.0)
INFECTION NOS	0	1 (0.9)	1 (0.5)	0	1 (1.2)	1 (1.0)
ABDOMINAL PAIN NOS	0	1 (0.9)	1 (0.5)	0	0	0
ADVERSE DRUG REACTION NOS	0	1 (0.9)	1 (0.5)	0	0	0
ANAEMIA NOS	1 (1.3)	0	1 (0.5)	0	0	0
ANXIETY DISORDER	1 (1.3)	0	1 (0.5)	0	0	0
ASTHMA AGGRAVATED	1 (1.3)	0	1 (0.5)	0	0	0
CARDIOPULMONARY FAILURE	1 (1.3)	0	1 (0.5)	0	0	0
CATHETER RELATED COMPLICATION	1 (1.3)	0	1 (0.5)	0	0	0
CELLULITIS GANGRENOUS	0	1 (0.9)	1 (0.5)	0	0	0

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Table 5g: Number (%) of Patients with SAEs in Studies 4, 5 and 16						
	Dalbavancin			Comparator		
Preferred term	1 dose N=75	2 doses N=113	Total N=188	7 days N=23	14 days N=81	Total N=104
Infections and Infestations						
Cellulitis†	2 (2.7)	0	**2(1.1)**	0	1 (1.2)	**1 (1)**
Cellulitis Gangrenous	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Bacteraemia	0	1 (0.9)	**1 (0.5)**	0	1 (1.2)	**1 (1)**
Infection NOS ¶	0	1 (0.9)	**1 (0.5)**	0	1 (1.2)	**1 (1)**
Osteomyelitis NOS ¶	0	1 (0.9)	**1 (0.5)**	0	1 (1.2)	**1 (1)**
Pneumonia NOS‡	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Lung Abscess NOS‡	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Interstitial pneumonia	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Postoperative wound infection†	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Wound Infection	0	0	**0**	1 (4.3)	0	**1 (1)**
Cardiac disorders						
Cardio-respiratory arrest*	0	2 (1.8)	**2(1.1)**	0	0	**0**
Cardiopulmonary Failure	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Cardiac Failure Congestive**	1 (1.3)	1 (0.9)	**2(1.1)**	0	0	**0**
Atrial fibrillation*	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Myocardial infarction**	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Respiratory/thoracic/mediastinal						
Respiratory failure (excluding neonatal)	0	2 (1.8)	**2(1.1)**	0	0	**0**
Asthma aggravated	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Pleural Effusion	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Gastrointestinal disorders						
Constipation	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Gastrointestinal haemorrhage NOS	0	0	**0**	1 (4.3)	0	**1 (1)**
Vomiting NOS	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Abdominal pain NOS §	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Pancreatitis chronic §	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Pancreatic pseudocyst	0	0	0	0	1 (1.2)	**1 (1)**
Gastric Varices	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Injury/ poisoning/procedural complic						
Catheter related complication	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Post procedural haemorrhage	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Hip Fracture	0	0	0	0	1 (1.2)	**1 (1)**
Overdose NOS	0	0	**0**	1 (4.3)	0	**1 (1)**
General disorders /infusion site conditions						
Adverse drug reaction NOS	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Pyrexia	1 (1.3)	1 (0.9)	**2(1.1)**	0	1 (1.2)	**1 (1)**
Blood and lymphatic system disorders*						
Febrile Neutropenia	0	2 (1.8)	**2(1.1)**	0	0	**0**
Anemia NOS	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Nervous system disorders						
Intracranial pressure increased NOS	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Dyskinesia	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Psychiatric disorders						
Mental status changes	0	0	0	0	1 (1.2)	**1 (1)**
Anxiety Disorder	1 (1.3)	0	**1 (0.5)**	0	0	**0**

2 SAEs in one subject: § (04035502); ¶ (16033014); ‡ (16004001); † (05002001); * (04038505); ** (05006010)

Table 5h: Number (%) of patients with SAEs in Studies 4, 5 and 16 (Continued)						
Preferred term	**Dalbavancin**			**Comparator**		
	1 dose N=146	**2 doses N=113**	**Total N=259**	**7 days N=23**	**14 days N=81**	**Total N=104**
Skin and subcutaneous tissue disorders						
Foot ulcer	0	0	**0**	0	1 (1.2)	**1 (1)**
Facial Edema	0	0	**0**	0	1 (1.2)	**1 (1)**
Vascular disorders						
Phlebitis NOS	0	0	**0**	0	1 (1.2)	**1 (1)**
Cerebrovascular accident NOS	0	0	**0**	0	1 (1.2)	**1 (1)**
Hepatobiliary disorders						
Cholecystitis acute NOS	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Congenital, familial and genetic disorders						
Sickle cell anaemia with crisis	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Metabolism and nutrition disorders						
Dehydration	0	1 (0.9)	**1 (0.5)**	0	0	**0**
Musculoskeletal/connective tissue disorders						
Inervetebral Disc Herniation	1 (1.3)	0	**1 (0.5)**	0	0	**0**
Renal and urinary disorders						
Renal failure acute	0	0	**0**	1 (4.3)	0	**1 (1)**
Neoplasms/ benign/ malignant /unspecified						
Gastric cancer NOS	0	0	**0**	1 (4.3)	0	**1 (1)**
Surgical and medical procedures						
Toe amputation	0	1 (0.9)	**1 (0.5)**	0	0	**0**

MO's Comment: *Overall, the incidence of SAEs was similar in dalbavancin -treated patients compared to comparator-treated patients. The most common SAE, cellulitis, occurred in 2 (2.7%) patients in studies 4, 5 and 16 who received a single dose of dalbavancin. Cellulitis was reported in 1(1%) subject who received 14 days of the comparator treatment. In the 2-dose dalbavancin subgroup 2 (1.8%) patients experienced cardio-respiratory arrest, 2 (1.8%) experienced respiratory failure, and another 2 (1.8%) experienced neutropenia. These were not reported in the comparator arm of these studies. The SAEs occurring in relatively high rates (>2%) in the comparator arm affected patients who received 7 days of comparator treatment. They developed such SAEs as wound infection, gastrointestinal hemorrhage NOS, overdose NOS, acute renal failure, and gastric cancer NOS; each of these SAEs was reported in one (4.3%) patient. The relative high rate is explained by the small number of patients in this sub-group (n= 23).*

Other SAEs: Phase 1 Studies

Of the 141 subjects who received dalbavancin in Phase 1, 2 (1.4%) had a total of 3 non-fatal SAEs as their AEs necessitated re-hospitalization or prolonged it. Subject 11-001-003, a 56-year-old black female received 500 mg dalbavancin; she had worsening coronary disease that required new drug therapy; the subject recovered with sequelae. Subject 11-001-011, was a 71-year-old Caucasian male who received 500 mg dalbavancin; he subsequently developed clotted dialysis access and a thrombosed right forearm. Both required new non-drug therapy but the subjects completely recovered from both events.

No SAEs occurred among the subjects who received placebo treatment.

Treatment-Related SAEs (Studies 8 and 9)

Table 6a is a summary of all treatment-related SAEs in studies 8 and 9 patients. Two (0.2%) dalbavancin-treated patients and 3 (0.6 %) who were comparator-treated developed a total of 6 SAEs considered by the sponsor to be treatment-related. Leukopenia occurred in 2 patients in the 2-dose subgroup of dalbavancin –treatment arm. No leukopenia occurred in the comparator arm. The other treatment-related SAEs included pancreatitis in a patient who received cefazolin treatment, thrombocytopenia in another, and pancytopenia in a third patient. The last two were linezolid-treated. The dalbavancin-treated subjects recovered completely without intervention. These SAEs occurred in < 1% of patients in either dalbavancin or the comparator arm.

Table 6a (Sponsor's Table 19): Treatment-Related SAEs in Studies 8 and 9 Patients

Preferred Term	Dalbavancin			Comparator		
Number (%) of Patients	1 Dose (n=344)	2 Doses (n=594)	Total (n= 938)	7 Days (n= 153)	14 days (n= 316)	Total (n= 469)
Leukopenia NOS	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Pancreatitis acute	0	0	**0**	1 (0.6)	0	**1 (0.2)**
Pancytopenia	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Thrombocytopenia	0	0	**0**	0	1 (0.3)	**1 (0.2)**

Treatment-related SAEs were defined as those reported as possibly or probably related to study treatment or AEs whose relationship was missing. Patients are counted only once at each level of summarization.

Dalbavancin-treated Patients with leukopenia

The sponsor's narratives of the patients with dalbavancin-related leukopenias are presented below, followed by the tables (6b and 6c) of their white blood cells (WBC) transition profiles. Other related tables are in appendix 6.

Patient 09-038-020, a 47-year-old Caucasian male treated with 2 doses of dalbavancin,

had mild leukopenia that was considered by the investigator to be probably related to study drug. At baseline, the patient's hematology parameters were within normal limits with the exception of elevated monocytes (16.1%). In a laboratory sample taken on Day 9, the patient's WBC count decreased from a baseline value of 6.9×103/μL to $4.0\times10^3/\mu L$.
At the EOT, assessment on Day 15, WBC count was $3.7\times10^3/\mu L$, and considered clinically significant by the investigator. At the EOT visit, the patient's neutrophils were 39.8%, lymphocytes were 38.8%, monocytes were 13.6%, eosinophils were 5.3%, and basophils were 2.5%. At the TOC visit on Day 29, the WBC count was within normal limits ($7.7 \times 10^3/ \mu L$). Monocytes remained elevated until the TOC visit. No action was taken regarding study treatment, and the patient recovered completely.

Table 6b **Patient 09-038-020 a 47-year-old Caucasian male, 2 doses of dalbavancin**

	Baseline	**Day 9**	**Day 15 (EOT)**	**Day 29 (TOC)**	**Comments**
WBC	6.9 x $10^3/\mu$	4.0 x $10^3/\mu$	3.7x $10^3/\mu$	7.7x $10^3/\mu$	No concurrent illness. Probably related. Recovered by Day 29. No further action taken.
Diff. (%)	63.4 S 16.1 M 17.1 L	45 S 12.2 M 4.2 E	39.8 S, 38.8 L, 13.6 M , 5.3E, 2.5 B	47.2 S 11.1 M 37.6 L, 2.7 E	
Normal range = 4.5 – 10.5 x $10^3/\mu$					

Patient 09-038-040, a 48-year-old Caucasian male treated with 2 doses of dalbavancin, had mild leukopenia that was considered by the investigator to be unlikely related to study drug; however, the sponsor considered the event to be possibly related to study drug. The patient had no relevant medical history; however, he did have a concurrent viral upper respiratory infection as evidenced by rhinorrhea and elevated lymphocytes. At baseline, hematology parameters were within normal limits, with the exception of decreased hemoglobin (Day -1 value 12.8 g/dL, normal range 14.0 to 18.0 g/dL). WBC at baseline was $9.3\times10^3/\mu L$ (normal range 4.5 to $10.5\times10^3/\mu L$), 16.9 % lymphocytes, and 72.5% neutrophils. The patient's hematology parameters remained stable (> baseline values of Hgb 12.8g/dL, Hct 35.7%, (normal Hgb 14-18g/dL, Hct 42-54%). At TOC (15 days after completion of study medication), the patient's WBC decreased to $2.6\times10^3/\mu L$ (65.8% lymphocytes, 24.3% neutrophils). The investigator attributed the abnormal laboratory values to the patient's viral upper respiratory infection. No action was taken regarding study treatment, and the patient was reported as completely recovered at Day 65.

Table 6c **Patient 09-038-040 a 48-year-old Caucasian male, 2 doses of dalbavancin**

	Baseline	**Day 8**	**Day 15 (EOT)**	**Day 29 (TOC)**	**Inv. Assessment**
WBC	9.3x $10^3/\mu$	7.0x $10^3/\mu$	6.9 x $10^3/\mu$	2.6x $10^3/\mu$	Pt. had viral URI. Unlikely related. Total recovery (D 65). No action taken.
Diff. (%)	72.5 S, 16.9 L, 9.7m 0.5E, plt 200	65.8 S 22.8L 2.6E plt 382	56.7S 34.0L 1.9E	24.3S, 65.8 L 6.5M 2.6E	
Normal range = 4.5 – 10.5 x $10^3/\mu$					

MO's Comment: *The reviewer agrees with the sponsor in considering leukopenia in the 47 year-old patient who received 2 doses of dalbavancin as probably dalbavancin-related. The temporal sequence of the administration of the drug to the development of the SAE without any other reported concomitant or associated event makes dalbavancin a strong suspect. On the contrary, although dalbavancin could have caused or contributed to leukopenia in the 48 year-old female patient who received 2 doses of dalbavancin and developed leukopenia by the 15th day, the time course of the upper respiratory infection (URI) to the laboratory development of leukopenia makes the URI a stronger suspect for the cause. The baseline WBC count was 9.3 x 10^{3}, with 16.9 % lymphocytes. In 2 weeks the WBC count decreased to 2.9 x 10^{3}, with a strong lymphocyte response from baseline level to* 65.8 %. *The patient reportedly recovered spontaneously by Day 65. This is not an uncommon clinical scenario.*

Treatment-Related SAEs (Studies 4, 5 and 16)

As shown in table 6d, there were no reported treatment-related SAEs in patients who received dalbavancin in studies 4, 5 and 16.

Table 6d Treatment-Related SAEs

Preferred Term	Dalbavancin			Comparator		
Number (%) of Patients	1 Dose (n=75)	2 Doses (n=113)	Total (n= 188)	7 Days (n= 23)	14 days (n=81)	Total (n=104)
Face edema	0	0	**0**	0	1 (1.2)	**1 (0.9)**
Renal failure acute	0	0	**0**	1 (4.3)	0	**1 (0.9)**

The two patients who developed treatment-related SAEs included a 63 year-old Caucasian female who developed acute renal failure after receiving 5 days of vancomycin. She recovered with sequelae. The second patient was a 19 year-old Hispanic female who developed facial edema during which period she received 3 different comparators. She required no intervention but recovered completely. These SAEs were considered by the sponsor as probably related to the drugs received.

MO comments: *No dalbavancin- treatment-related SAEs among studies 4, 5 and 16 were reported.*

Treatment-Related SAEs in Phase 1

There were no treatment-related SAEs in Phase 1

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall Profile of Dropouts

The patients whose study treatments were discontinued were grouped by the investigators/sponsor into the following categories:

- Discontinued because of adverse events
- Lost to follow up
- Treatment failures/ worsening clinical status
- Withdrew for reasons other than adverse events
- Withdrawn at the investigator's discretion
- Non-compliant to medication
- Withdrew Consent
- Other reasons
- Deaths

Table 7a shows the dropout profiles of studies 8 and 9. The subset of patients from whom adverse events of the study drug can be most reliably ascertained in this section is the subset of patients that dropped out due to adverse events.

Table 7a: Dropout Profiles in Studies 8 and 9

Characteristics	**Dalbavancin (N = 938)**						**Comparator (N = 469)**					
	1 dose n =344	**%**	**2 doses n =594**	**%**	**Total n=938**	**%**	**7 days n =153**	**%**	**14days n =316**	**%**	**Total n=469**	**%**
Completed study					**831**	**88.6**					**423**	**%**
Dropout Due to ≥ one AE(s)	12	3.5	4	0.7	**16**	**1.7**	3	2.0	1	0.3	**4**	**0.9**
Study Med D/C'd due to AE	28	8.1	7	1.2	**35**	**3.7**	6	3.9	6	1.9	**12**	**2.6**
Lost to follow up	33	9.6	29	4.9	**62**	**6.6**	17	11.1	16	5.1	**33**	**7.1**
Died	3	0.9	2	0.3	**5**	**0.5**	2	1.3	3	1.0	**5**	**1.1**
Withdrew Consent	22	6.4	5	0.8	**27**	**2.9**	2	1.3	3	1.0	**5**	**1.1**
Dropout for Other reasons	10	2.9	3	0.5	**13**	**1.4**	**3**	**2.0**	**2**	**0.6**	**5**	**1.1**
Treatment failures	16	4.7	0	-	**16**	**1.7**	6	3.9	0	-	**6**	**1.3**
Investigator's discretion	6	1.7	0	-	**6**	**0.6**	5	3.3	1	0.3	**6**	**1.4**
D/C'd = discontinued												

MO's Comments: *Table 7a shows the dropout profiles of patients in studies 8 and 9. Among the patients who were discontinued from study secondary to at least one AE, the rate of discontinuations in the overall dalbavancin arm (1.7 %) was slightly higher than the overall comparator group (0.9 %).The numbers were small, particularly in the comparator arm. Nevertheless, within the subgroups, there was a higher dropout rate*

among patients who received one dose of dalbavancin (3.5%) compared to patients who received 2 doses of dalbavancin (0.7%), patients who received 7 days of comparator (2.0%), or 14 days of the comparator (0.3%). The reason(s) for a higher rate of AEs in those who received 1 dose is/are unclear. Table 7b1 and 7b2 display the reasons listed by the sponsors for patients that dropped out for "Other Reasons". The kind of reasons and frequencies of them are fairly comparable across study arms although only those reasons given for dalbavancin are listed by the reviewer in table 7b2

Table 7b1

Distribution of Patients Who dropped Out for "Other Reasons" in Studies 8 and 9											
1 dose n =344	**%**	**2 doses n =594**	**%**	**Total n=938**	**%**	**7 days n =153**	**%**	**14days n =316**	**%**	**Total n=469**	**%**
10	2.9	3	0.5	**13**	**1.4**	**3**	**2.0**	**2**	**0.6**	**5**	**1.1**

Table 7b2: Dalbavancin -Treated Patients in Studies 8 and 9 Who Dropped Out for "Other Reasons".

PTID	**№ of doses**	**Reason for Discontinuation From Study**
09008043	2	PATIENT NEVER RETURNED FOR TEST OF CURE
09025042	2	WORSENING OF SSTI SYMPTOMS
09063010	2	SERIOUS ADVERSE EVENT
09005093	1	PT WAS WITHDRAWN FROM THE STUDY DUE TO OSTEOMYELITIS.
09009001	1	PROTOCOL CONTRADICTION
09025032	1	PATIENT INVOLVED IN REHAB PROGRAM
09025056	1	PATIENT REMOVED FROM STUDY BY PRIMARY CARE PHYSICIAN
09057004	1	LATER DROPPED BECAUSE EXCLUSION CRITERION (OSTEO) MET
09067006	1	WORSENING STUDY SITE INFECTION
08033028	1	SAE/SEPSIS
08050007	1	HOSPITALIZED FOR NECROTIZING FASCITIS; NO EOT,TOC VISITS
08061007	1	ADVERSE EVENT
08083011	1	PRIMARY MD WANTED MRSA COVERAGE

Dropout Profiles in Studies 4, 5 and 16

As shown in table 7c, the dropout profiles in studies 4, 5 and 16 were similar to those in studies 8 and 9 except that the figures were smaller in studies 4, 5 and 16. One (1.3 %) patient who received 1 dose of dalbavancin dropped out because of AEs. There were more dropouts from the comparator arm due to AEs although the numbers in both treatment arms were small. None in the 2-dose group reported any AE leading to discontinuation. Two (8.7%) of patients who received 7 days of the comparator dropped out from study while none in the 14 days subgroup experienced any AE leading to discontinuation. Thus 0.5% of patients in the dalbavancin arm had at least one AE while 1.9 % in the comparator group had at least one AE leading to discontinuation from study. As shown in table 7d2, of the 2 (2.7%) dalbavancin-treated patients who did not complete study, one was discontinued for worsening clinical status and the other did not show up for TOC visit.

Table 7c : Dropout Profiles in Studies 4, 5 and 16

Characteristics	Dalbavancin N = 188						Comparator N = 104					
	1 dose n =75	%	2 doses n =113	%	Total n=188	%	7 days n =23	%	14 days n =81	%	Total n=104	%
Dropout Due to AEs	1	1.3	0	-	**1**	**0.5**	2	8.7	0	-	**2**	**1.9**
Lost to follow up	4	5.3	3	2.7	**7**	**3.7**	1	4.3	4	4.9	**5**	**4.8**
Died	2	2.7	1	0.9	**3**	**1.6**	2	8.7	0	-	**2**	**1.9**
Withdrew Consent	0	-	0	-	**0**	**-**	2	8.7	0	-	**2**	**1.9**
Dropout for Other reasons	3	4	0	-	**4**	**2.1**	1	4.4	1	1.2	**2**	**1.9**
Treatment failures	1	1.3	0	-	**1**	**0.5**	1	4.4	1	1.2	**2**	**1.9**
Investigator's discretion	0	-	0	-	**0**	**-**	2	8.7	1	1.2	**3**	**2.9**
Prohibited concomitant med	1	1.3	0	-	**1**	**0.5**	0	-	**0**	**-**	**0**	**-**
Non-compliant	2	-	0	-	**2**	**1.0**	0	-	**0**	**-**	**0**	**-**

Table 7d1: Patients Who dropped Out for "Other Reasons" in Studies 4, 5 and 16

1 dose n =75	%	2 doses n =113	%	Total n=188	%	7 days n =23	%	14 days n =81	%	Total n=104	%
2	2.7	0	-	**3**	**1.6**	**6**	**26**	**2**	**2.5**	**8**	**7.7**

Table 7d2 Dalbavancin –Treated Patients in Studies 4, 5 and 16 "Other Reasons" for Dropouts

PTID	№ of doses	Reason for Discontinuation From Study
16038007	1	DID NOT COMPLETE TEST OF CURE VISIT
16044014	1	WORSENING CLINICAL STATUS

Dropout Profiles in Phase 1

There were no reports of subjects who were discontinued from study due to an AE in Phase 1 studies.

7.1.3.2 Specific Adverse events associated with dropouts

AEs Leading to Discontinuation from Studies 8 and 9

Table 7e shows the distribution of patients across study arms who were withdrawn from study due to an AE. Osteomyelitis, reported by 3 (0.3%) dalbavancin-treated patients and 1 (0.2%) comparator-treated patient was the AE that led to the study withdrawal for more than 1 patient in any treatment arm. Table 7f is a continuation of Table 7e.

AEs Leading to Discontinuation from Studies 4, 5 and 16

As shown in table 7e, 1 (1.3%) patient who received one dose of dalbavancin who had Escherichia urinary tract infection, was withdrawn from the study. The other two patients who were withdrawn were comparator-treated and had either pneumonia or urticaria.

MO comments: *As indicated in the reviewer's comment on Table 7a (above)**,** the overall dropout rate secondary to an AE was slightly higher on the dalbavancin arm (1.7%) compared to the comparator arm (0.9%). The numbers were small and inadequate to make any inferences. The only AE that led to the discontinuation or withdrawal of more than one patient from this study group was osteomyelitis which occurred at rate of 0.3% in the dalbavancin arm and at 0.2% in the comparator arm. Each of the other AEs listed in tables 7e and 7f affected one patient across the study arms.*

AEs Leading to Discontinuation from Phase 1 studies.

There were no AE-related dropouts in Phase 1 studies.

Table 7e (Modified Sponsor's table B.9): Adverse Events Leading to Withdrawal from Studies 8 and 9

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
Number (%) of patients with at least one AE leading to withdrawal	12 (3.5)	4 (0.7)	16 (1.7)	3 (2.0)	1 (0.3)	4 (0.9)
OSTEOMYELITIS NOS	2 (0.6)	1 (0.2)	3 (0.3)	1 (0.7)	0	1 (0.2)
CARDIAC ARREST	0	1 (0.2)	1 (0.1)	1 (0.7)	0	1 (0.2)
ANXIETY	1 (0.3)	0	1 (0.1)	0	0	0
CARDIAC DEATH	1 (0.3)	0	1 (0.1)	0	0	0
CARDIOGENIC SHOCK	1 (0.3)	0	1 (0.1)	0	0	0
CARDIOPULMONARY FAILURE	1 (0.3)	0	1 (0.1)	0	0	0
CELLULITIS	1 (0.3)	0	1 (0.1)	0	0	0
INFECTION NOS	1 (0.3)	0	1 (0.1)	0	0	0
INJECTION SITE PAIN	1 (0.3)	0	1 (0.1)	0	0	0
LEUKOCYTOSIS	0	1 (0.2)	1 (0.1)	0	0	0
LYMPH NODE PAIN	1 (0.3)	0	1 (0.1)	0	0	0
MUSCLE CRAMP	1 (0.3)	0	1 (0.1)	0	0	0
MUSCULOSKELETAL STIFFNESS	1 (0.3)	0	1 (0.1)	0	0	0
MYOCARDIAL INFARCTION	0	1 (0.2)	1 (0.1)	0	0	0
NECROTISING FASCIITIS NOS	1 (0.3)	0	1 (0.1)	0	0	0
SKIN AND SUBCUTANEOUS TISSUE ABSCESS NOS	1 (0.3)	0	1 (0.1)	0	0	0

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Table 7f (Modified Sponsor's table B.9): Adverse Events Leading to Withdrawal from Studies 8 and 9

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
URTICARIA NOS	1 (0.3)	0	1 (0.1)	0	0	0
ARTHRITIS INFECTIVE NOS	0	0	0	1 (0.7)	0	1 (0.2)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0	0	0	0	1 (0.3)	1 (0.2)
NAUSEA	0	0	0	1 (0.7)	0	1 (0.2)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Table 7g (Modified Sponsor's table B.10) Adverse Events Leading to Withdrawal from Studies 4, 5 and 16

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
Number (%) of patients with at least one AE leading to withdrawal	1 (1.3)	0	1 (0.5)	2 (8.7)	0	2 (1.9)
ESCHERICHIA URINARY TRACT INFECTION	1 (1.3)	0	1 (0.5)	0	0	0
PNEUMONIA NOS	0	0	0	1 (4.3)	0	1 (1.0)
URTICARIA NOS	0	0	0	1 (4.3)	0	1 (1.0)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

7. 1.3.3 Other Significant Adverse Events Leading to Discontinuation of study medication (Studies 8 and 9)

Table 7f displays significant AEs in studies 8 and 9 which necessitated discontinuation of study medication.

Skin rash was the most common AE necessitating drug discontinuation and occurred, overall, in 5 (0.5%) patients who were dalbavancin-treated and in 2 (0.4%) patients who were comparator-treated. Thus, the rates of occurrence of these AEs in the 2 study arms were similar. Within the subgroups, 3 (0.9%) patients who received 1 dose of dalbavancin compared to 1 (0.7%) patient who received 7 days of the comparator treatment developed rash. Similarly, 2 (0.3%) patients who received 2 doses of dalbavancin and 1 (0.3%) who received 14 days of comparator treatment developed rash. The AE of skin rash occurred at similar rates in both study arms.

The skin rash of each dalbavancin-treated patient was described in the CRF as mild or moderate, flat red and "from neck to the leg" (in one case). No additional information was provided about the other physical characteristics of the rash. The eruptions developed on Day 2 in 2 patients treated with 1 dose of dalbavancin and on Day 4 in the third patient in this sub-group. For the 2 patients who received the 2-dose regimen of dalbavancin, the onset of rash was on Day 8 in one patient and on Day 10 in the other.

In the comparator arm, the patient who was to receive treatment for 7 days developed rash Day 3 into treatment; the patient in the 14-day subgroup developed rash on Day 13 into treatment.

In addition to Table 7f which shows the more frequent significant AEs leading to discontinuation of study medications (i.e. osteomyelitis, cellulitis, diarrhea, etc), the other less frequently occurring AEs are shown in the Appendix tables (Appendix 7).

Other Significant Adverse Events Leading to Discontinuation of study medication (Studies 4, 5 and 16)

Table 7g shows the AEs leading to discontinuation of medication in studies 4, 5 and 16. Overall, the patients who developed significant AEs in this study group were relatively few.

Four (2.1%) dalbavancin-treated patients had significant AEs compared to 10 (9.6%) patients who were comparator-treated. Within the subgroups, all 4 patients who had AEs in the dalbavancin arm received 1dose. None who received 2 doses of dalbavancin developed AEs. In the comparator arm, 7 (30.4%) patients in the 7-day subgroup developed significant AEs compared to 3 (3.7%) who received 14 days of comparator treatment. The rates of AEs were higher in the comparator arm than in the dalbavancin treatment arm.

Table 7f (Modified Sponsor's table B.5): Adverse Events Leading to Discontinuation of Study Medication (Studies 8 and 9)

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
Number (%) of patients with at least one AE leading to discontinuation	29 (8.4)	6 (1.0)	35 (3.7)	6 (3.9)	6 (1.9)	12 (2.6)
RASH NOS	3 (0.9)	2 (0.3)	5 (0.5)	1 (0.7)	1 (0.3)	2 (0.4)
OSTEOMYELITIS NOS	4 (1.2)	0	4 (0.4)	0	0	0
CELLULITIS	2 (0.6)	0	2 (0.2)	1 (0.7)	0	1 (0.2)
DIARRHOEA NOS	2 (0.6)	0	2 (0.2)	1 (0.7)	0	1 (0.2)
INFECTION NOS	2 (0.6)	0	2 (0.2)	0	0	0
INSOMNIA	1 (0.3)	1 (0.2)	2 (0.2)	0	0	0
RASH GENERALISED	2 (0.6)	0	2 (0.2)	0	0	0
SKIN AND SUBCUTANEOUS TISSUE ABSCESS NOS	2 (0.6)	0	2 (0.2)	0	0	0
NAUSEA	1 (0.3)	0	1 (0.1)	2 (1.3)	0	2 (0.4)
PNEUMONIA NOS	0	1 (0.2)	1 (0.1)	1 (0.7)	0	1 (0.2)
ABDOMINAL PAIN UPPER	0	1 (0.2)	1 (0.1)	0	0	0
ABSCESS LIMB	1 (0.3)	0	1 (0.1)	0	0	0
ACCIDENTAL OVERDOSE	1 (0.3)	0	1 (0.1)	0	0	0
ADVERSE DRUG REACTION NOS	1 (0.3)	0	1 (0.1)	0	0	0
ARTHRITIS BACTERIAL	1 (0.3)	0	1 (0.1)	0	0	0
BACTERAEMIA	1 (0.3)	0	1 (0.1)	0	0	0

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Table 7g (Modified Sponsor's table B.6): Adverse Events Leading to Discontinuation of Study Medication in studies 4, 5 and 6

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
Number (%) of patients with at least one AE leading to discontinuation	4 (5.3)	0	4 (2.1)	7 (30.4)	3 (3.7)	10 (9.6)
BLISTER	1 (1.3)	0	1 (0.5)	0	0	0
CELLULITIS	1 (1.3)	0	1 (0.5)	0	0	0
ESCHERICHIA URINARY TRACT INFECTION	1 (1.3)	0	1 (0.5)	0	0	0
GENERALISED ERYTHEMA	1 (1.3)	0	1 (0.5)	0	0	0
PRURITUS	1 (1.3)	0	1 (0.5)	0	0	0
URINARY TRACT INFECTION NOS	1 (1.3)	0	1 (0.5)	0	0	0
NAUSEA	0	0	0	2 (8.7)	0	2 (1.9)
URTICARIA NOS	0	0	0	1 (4.3)	1 (1.2)	2 (1.9)
ANTIBIOTIC LEVEL NOS ABOVE THERAPEUTIC	0	0	0	1 (4.3)	0	1 (1.0)
CEREBROVASCULAR ACCIDENT NOS	0	0	0	0	1 (1.2)	1 (1.0)
FLUSHING	0	0	0	1 (4.3)	0	1 (1.0)
PNEUMONIA NOS	0	0	0	1 (4.3)	0	1 (1.0)
PSEUDOMONAS INFECTION NOS	0	0	0	0	1 (1.2)	1 (1.0)
RED MAN SYNDROME	0	0	0	1 (4.3)	0	1 (1.0)
RENAL FAILURE ACUTE	0	0	0	1 (4.3)	0	1 (1.0)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Other Significant Adverse Events in Phase 1 studies

There were 3 subjects who had AEs that led to discontinuation of study drug; there was an additional subject who had a notable AE (see table 7h). The sponsor's narratives of the 3 subjects who had AEs that led to discontinuation of study drugs as well as the 4th subject who had "a notable AE" are as follows:

Subject 02-100-136, a 22-year-old black female, had a mild allergic reaction (WHO toxicity Grade 1) during infusion of a single 840-mg dose of dalbavancin. At 25 minutes of the 30-minute infusion, the subject developed urticarial lesions (hives) on her face and arms, complained of chills, and had goose bumps on her arms. There was no respiratory distress, no wheezing, and no hoarseness or lip edema. Study drug infusion was discontinued, and the subject completely recovered within 45 minutes after receiving a single IV dose of diphenhydramine 25 mg. The investigator considered the event to be probably related to study drug. The subject recovered completely.

Subject 12-001-020, a 49-year-old black female with normal hepatic function who received a single 1000-mg dose of dalbavancin, had severe constipation Days 2 to 8 into treatment; the subject had no pertinent medical history. The subject's chronic and on-going concomitant medications at the time of the event included atenolol and hydrochlorothiazide/ triamterene. The subject received magnesium citrate on Day 7 and recovered completely. The subject did not receive her second dose of study drug on Day 8 due to the constipation. The constipation was considered by the investigator to be possibly related to study drug. The subject recovered completely.

Subject 13-001-020, a 50-year-old Caucasian female who received a single 1000-mg dose of dalbavancin, had a mild allergic reaction during study drug infusion that resulted in premature discontinuation of the study drug after 21 minutes of the 30-minute infusion. The patient's allergic reaction was characterized by sneezing, coughing, facial flushing, and watery eyes, which continued for 5 days. The subject did not require treatment for this event. The investigator considered the event to be possibly related to study drug. The subject recovered completely.

Table 7h Dropout and Study Medication Discontinuation Profile in Phase 1

PTID	Treatment received	Reason treatment discontinued
12001020	Dalbavancin 1000 mg	Constipation and Subject / Investigator request
13001020	Dalbavancin 500-1000 mg	Drug Hypersensitivity
02100136	Dalbavancin 500-1000 mg	Drug Hypersensitivity
The patient with a notable rash that did not lead to discontinuation of study medication.		
13001018	Dalbavancin 500-1000 mg	Moderate morbilliform rash

The following subject developed this clinical event which the sponsor described "a notable AE":
Subject 13-001-018, a 69-year-old Caucasian female with normal renal function who received a single 1000-mg dose of dalbavancin, had a morbilliform rash of moderate

severity, which began 10 days after study drug infusion. When the subject returned to the clinic for the Day 14 follow-up, the redness was subsiding. The subject was referred to a dermatologist who prescribed a methyl prednisolone dose pack and loratadine, which continued for 6 and 7 days, respectively. The itching and rash resolved after 8 days (on Day 18). The subject reported intermittent flushing and itching that continued for several weeks. The event resolved completely without sequelae by Day 59. The investigator considered the rash to be probably related to study drug. The subject recovered completely.

7.1.4 Other Search Strategies

The following were sought for guidance to help the reviewer's sensitivity for detection of additional potential safety signals in the study data submitted:

1. Literature Review

Literature review was done to ascertain safety issues that are considered generic to the glycopeptide class of antibiotics which might also be found in patients treated with dalbavancin (a lipoglycopepetide).

Two well known examples of AEs associated with glycopeptides are ototoxicity and nephrotoxicity.

2. General Toxicology and Animal Data

Toxicology study review by Dr. Wendelyn Schmidt for this NDA reported the following toxic effects in rats and dogs who received daily dalbavancin for up to 3 months duration:

- Histamine-like response
- Persistent liver enzyme (AST/ALT) elevations
- Hepatocellular necrosis/ vacuolization/degeneration
- Persistent elevations in Blood Urea Nitrogen (BUN)
- Renal tubular vacuolization/degeneration/ necrosis
- Pancreatic (acinar cells) vacuolization/degeneration/ apoptosis

And the following affected dogs only:

- Persistent RBC decreases (up to one year post-dose)

7.1.5 Common Adverse Events

Common Adverse Events Reported in >2% of the Patients in studies 8 and 9

AEs occurring in 2% or more of patients in any treatment arm in studies 8 and 9 are presented by preferred term in decreasing order of frequency in Table 8a.
Most of the AEs reported were described by the sponsor as "unrelated" or "unlikely related" to study drugs. However, all AEs were regarded as treatment -emergent to allow conservative analysis of the data provided and comparison between AEs reported in both arms of the studies.

Overall, 458 (49%) dalbavancin-treated patients reported at least 1 AE, similar to 243 (51.8%) of comparator-treated patients. Among patients who received 1 dose of dalbavancin, 122 (35.5%) had at least one AE, similar in rate to 57 (37.3%) patients who received 7 days of the comparator treatment. Also, 336 (56.6%) patients who received 2 doses of dalbavancin had AEs compared to 186 (58.9%) who received comparator treatment.

The frequency of AEs was generally higher in patients who received 2 doses of dalbavancin treatment or 14 days of comparator treatment compared to patients who received 1 dose of dalbavancin or 7 days of comparator treatment respectively.

MO's Comment: *There may or may not be a direct relationship between the extent of drug exposure (the number of doses or the duration of treatment) received to the likelihood of development of an AE. The differences in rates of AEs between shorter and longer durations of treatment may have been related to some patients being sicker, and having other complicating factors (co-morbid conditions, concomitant medications, etc) which necessitated longer treatments.*

The Three Most Common of the Common AEs

Nausea, headache, and diarrhea were the 3 most commonly reported AEs for both treatment groups although less frequently in dalbavancin-treated subjects than in comparator-treated patients.

Nausea: There was a smaller proportion of patients in the dalbavancin arm [52(5.5%)] who reported nausea than in the comparator arm [39 (8.3%)]. Fifteen (4.4%) patients who received 1 dose of dalbavancin reported nausea compared to 9 (5.9%) who received 7 days of the comparator; 37 (6.2%) who received 2 doses of dalbavancin compared to 29 (9.2%) who received 14 days reported nausea.

Of the patients who received dalbavancin who reported nausea, 32 (73%) was of mild intensity, 11 (25 %) was moderate, and 1 (~2%) was severe. In the comparator group, 28 (72 %) was of mild intensity and 11 (28%) was of moderate intensity.

Headache: Of the 52 (5.5%) dalbavancin-treated subjects who reported headache, 13 (3.8%) received 1 dose and 39 (6.6 %) received 2 doses. Of all dalbavancin –treated patients who reported headache, 35 (63%) reported that it was mild in intensity, moderate in 15 (29%) and severe in 4 (7.7 %). Of the 32 comparator-treated patients who reported headache, the headache was of mild intensity in 17 (53.1%), moderate in 14 (43.8%), and severe in 1 (3.1%).

Diarrhea: Forty three (4.6%) dalbavancin-treated patients reported diarrhea out of which 15 (4.4%) received 1 dose, and 28 (4.7%), 2 doses. Of those who reported diarrhea, 35 (81.4%) reported it as mild in intensity, 7 (16%) as moderate, and 1 (2.3%) as severe. Twenty seven (5.8%) of the comparator- treated patients reported diarrhea; 5 (3.3%) received 7 days of treatment, and 22 (7.0%) received 14 days. The diarrhea was reported

as mild in intensity in 23/27 (85%), and moderate in 4/27 (15%). No severe diarrhea was reported.

The rest of the common AEs are as shown in tables 8a and 8b.

MO's Comment: *Aside from headache, the most frequently reported AEs among the patients in both the dalbavancin and the comparator groups (table 8a) comprise nausea, diarrhea, vomiting and constipation. These gastrointestinal-related AEs occurred at the same or slightly higher frequencies in the comparator arm of the study than among the patients that received dalbavancin. On the contrary, although the numbers are relatively small, the incidence of anemia, slightly higher among the dalbavancin-treated patients than the comparator-treated patients, is notable. Given Dr. Schmidt's evaluation of animal toxicology data reporting the "Persistent RBC decreases (up to one year post-dose)" in rats and dogs that received daily dalbavancin for up to 3 months duration, the reviewer will explore the possibility of anemia as a possible significant safety issue in greater detail during the review of the possible drug effects on hematology parameters.*

Table 8a (Sponsor's table B.3): **Adverse Events Reported in >2% of the Patients (studies 8 and 9)**

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
Number (%) of patients with at least one AE	122 (35.5)	336 (56.6)	458 (48.8)	57 (37.3)	186 (58.9)	243 (51.8)
NAUSEA	15 (4.4)	37 (6.2)	52 (5.5)	9 (5.9)	30 (9.5)	39 (8.3)
HEADACHE	13 (3.8)	39 (6.6)	52 (5.5)	4 (2.6)	28 (8.9)	32 (6.6)
DIARRHOEA NOS	15 (4.4)	28 (4.7)	43 (4.6)	5 (3.3)	22 (7.0)	27 (5.8)
VOMITING NOS	8 (2.3)	23 (3.9)	31 (3.3)	4 (2.6)	13 (4.1)	17 (3.6)
CONSTIPATION	5 (1.5)	26 (4.4)	31 (3.3)	2 (1.3)	10 (3.2)	12 (2.6)
URINARY TRACT INFECTION NOS	4 (1.2)	23 (3.9)	27 (2.9)	1 (0.7)	9 (2.8)	10 (2.1)
PRURITUS	8 (2.3)	15 (2.5)	23 (2.5)	4 (2.6)	5 (1.6)	9 (1.9)
ANAEMIA NOS	6 (1.7)	17 (2.9)	23 (2.5)	1 (0.7)	4 (1.3)	5 (1.1)
RASH NOS	7 (2.0)	13 (2.2)	20 (2.1)	4 (2.6)	9 (2.8)	13 (2.8)
INSOMNIA	4 (1.2)	14 (2.4)	18 (1.9)	4 (2.6)	17 (5.4)	21 (4.5)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	4 (1.2)	14 (2.4)	18 (1.9)	1 (0.7)	11 (3.5)	12 (2.6)
BLOOD LACTATE DEHYDROGENASE INCREASED	5 (1.5)	12 (2.0)	17 (1.8)	0	9 (2.8)	9 (1.9)
DYSPEPSIA	2 (0.6)	12 (2.0)	14 (1.5)	2 (1.3)	3 (0.9)	5 (1.1)
LIVER FUNCTION TEST ABNORMAL	1 (0.3)	13 (2.2)	14 (1.5)	0	5 (1.6)	5 (1.1)
HYPERGLYCAEMIA NOS	0	13 (2.2)	13 (1.4)	0	8 (2.5)	8 (1.7)
HYPOGLYCAEMIA NOS	0	11 (1.9)	11 (1.2)	1 (0.7)	7 (2.2)	8 (1.7)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Table 8b (8a-Cont'd; Sponsor's Table B.3): Adverse Events Reported in >2% of the Patients (studies 8 and 9)

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
ALANINE AMINOTRANSFERASE INCREASED	2 (0.6)	7 (1.2)	9 (1.0)	3 (2.0)	9 (2.8)	12 (2.6)
ABDOMINAL PAIN NOS	1 (0.3)	8 (1.3)	9 (1.0)	4 (2.6)	4 (1.3)	8 (1.7)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (0.6)	3 (0.5)	5 (0.5)	4 (2.6)	3 (0.9)	7 (1.5)
FATIGUE	0	5 (0.8)	5 (0.5)	4 (2.6)	3 (0.9)	7 (1.5)
LOOSE STOOLS	0	3 (0.5)	3 (0.3)	1 (0.7)	11 (3.5)	12 (2.6)
THROMBOCYTOPENIA	0	1 (0.2)	1 (0.1)	1 (0.7)	7 (2.2)	8 (1.7)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Common Adverse Events Reported in >2% of the Patients in studies 4, 5 and 16

Diarrhea NOS, nausea and abdominal pain were the 3 most commonly reported AEs for both treatment arms in this study group (see table 8c)

Diarrhea NOS
Twenty (10.6 %) dalbavancin-treated patients reported diarrhea out of which 9 (12.0%) received 1 dose, and 11 (9.7%), 2 doses. The diarrhea did not seem to be dose-related. Twelve (11.5%) of the comparator- treated patients in this study group reported diarrhea, 3 (13.0%) in the patients that received 7 days of treatment, and 9 (11.1%) in the subgroup that received 14 days. In the dalbavancin group, the diarrhea was mild in intensity in 14/20 (70%), moderate in 5/20 (25%) and severe in 1(5%). Of the comparator-treated patients, diarrhea was reported as mild in 9/12 (75%) and moderate in 3/12 (25%) of reported cases. No severe diarrhea was reported.

Nausea: In this study group, 17 (9.0%) patients in the dalbavancin arm reported nausea compared to 9 (8.7%) in the comparator arm. In the subgroups, nausea was reported in 4 (5.3%) patients who received 1 dose of dalbavancin, in comparison to 3 (13.0%) who received 7 days of the comparator treatment. Of the patients who received 2 doses of dalbavancin, 13 (11.5%) reported nausea compared to 6 (7.4%) of patients who received 14 days of comparator treatment.

Of the patients who received dalbavancin in this study group, 12/17 (71%) reported their nausea to be of mild intensity and 5/17 (29%) of moderate intensity. On the comparator side, 4/9 (44.4%) reported their nausea to be mild in intensity and 5 (55.5%) to be of moderate intensity. None reported severe nausea.

MO's Comment: *In studies 4, 5 and 16, the reported gastrointestinal-related AEs (diarrhea, nausea, vomiting, constipation, and abdominal pain) occurred as the most common and at comparable rates among the dalbavancin-treated and the comparator-treated groups. While the frequency of anemia was higher among the comparator-treated patients than dalbavancin-treated group (table 8c), the opposite is the case in the studies 8 and 9 (table 8a). Again, the numbers are too small to allow the drawing of meaningful inferences.*

Table 8c (Sponsor's table B.4): Adverse Events Reported in >2% of the Patients (studies 4, 5 and 16)

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
Number (%) of patients with at least one AE	47 (62.7)	80 (70.8)	127 (67.6)	16 (69.6)	67 (82.7)	83 (79.8)
DIARRHOEA NOS	9 (12.0)	11 (9.7)	20 (10.6)	3 (13.0)	9 (11.1)	12 (11.5)
NAUSEA	4 (5.3)	13 (11.5)	17 (9.0)	3 (13.0)	6 (7.4)	9 (8.7)
ABDOMINAL PAIN NOS	2 (2.7)	9 (8.0)	11 (5.9)	0	1 (1.2)	1 (1.0)
VOMITING NOS	2 (2.7)	7 (6.2)	9 (4.8)	2 (8.7)	7 (8.6)	9 (8.7)
CONSTIPATION	1 (1.3)	8 (7.1)	9 (4.8)	0	7 (8.6)	7 (6.7)
HYPOTENSION NOS	3 (4.0)	6 (5.3)	9 (4.8)	0	2 (2.5)	2 (1.9)
RASH NOS	2 (2.7)	7 (6.2)	9 (4.8)	0	0	0
ANAEMIA NOS	2 (2.7)	6 (5.3)	8 (4.3)	1 (4.3)	6 (7.4)	7 (6.7)
FATIGUE	5 (6.7)	3 (2.7)	8 (4.3)	0	6 (7.4)	6 (5.8)
PYREXIA	1 (1.3)	7 (6.2)	8 (4.3)	0	5 (6.2)	5 (4.8)
HYPERGLYCAEMIA NOS	3 (4.0)	5 (4.4)	8 (4.3)	1 (4.3)	3 (3.7)	4 (3.8)
PAIN IN LIMB	2 (2.7)	5 (4.4)	7 (3.7)	0	4 (4.9)	4 (3.8)
HYPOKALAEMIA	0	7 (6.2)	7 (3.7)	1 (4.3)	1 (1.2)	2 (1.9)
URINARY TRACT INFECTION NOS	1 (1.3)	6 (5.3)	7 (3.7)	0	2 (2.5)	2 (1.9)
DYSPNOEA NOS	1 (1.3)	6 (5.3)	7 (3.7)	0	1 (1.2)	1 (1.0)
HYPOGLYCAEMIA NOS	2 (2.7)	4 (3.5)	6 (3.2)	1 (4.3)	2 (2.5)	3 (2.9)
BACK PAIN	0	6 (5.3)	6 (3.2)	0	2 (2.5)	2 (1.9)
COUGH	3 (4.0)	3 (2.7)	6 (3.2)	0	2 (2.5)	2 (1.9)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Common Adverse Events Reported in >2% in Phase 1 studies

Table 8d is the sponsor's table of AEs occurring in 2.0 % or more of the overall Phase 1 study subjects who received dalbavancin presented by MedDRA preferred term in decreasing order of frequency.
Approximately 74.5% of subjects who received dalbavancin reported at least 1 AE, compared to 78.9% who received placebo.

The 2 most commonly reported AEs were pyrexia and headache.

Pyrexia was reported by 21/141 (14.9%) patients who received dalbavancin compared to 5/19 (26.3%) patients who received placebo. Pyrexia was reported as mild in 20/21 (95.2%) dalbavancin-treated patients, and moderate in 1/21 (4.8%). The latter received 350 mg dalbavancin. No case of pyrexia was reported as severe. In all 5 subjects who received placebo, pyrexia was reported as mild.

Headache was reported by 18/141 (12.8%) subjects who received dalbavancin and 4/19 (21.1%) subjects who received placebo. Seventeen (94.4%) of dalbavancin-treated subjects reported their headaches as mild; 1 subject who received 1000 mg dalbavancin had a headache of moderate intensity (Subject 13001006).

Other commonly reported AEs (frequency >5%) among dalbavancin–treated patients were upper respiratory tract infection, back pain, nausea, and pharyngolaryngeal pain. The frequency of each of these events was higher in subjects who received dalbavancin than in those who received placebo.

Two commonly reported AEs, diarrhea and fatigue, were reported with a greater frequency (>10%) in the highest dose group of dalbavancin compared with the lower dalbavancin dose groups.

Diarrhea was reported by 5/34 (14.7%) subjects who received >1000 mg of dalbavancin, 1/78 (1.3%) subject who received 630 mg dalbavancin, 1/29 (3.4%) subject who received 140 mg of dalbavancin, and 1/19 (5.3%) subject who received placebo. All AEs of diarrhea were mild or moderate in intensity and resolved completely.

Fatigue was reported by 5/34 (14.7%) subjects who received >1000 mg of dalbavancin, 1/78 (1.3%) subject who received 1000 mg of dalbavancin and 1/19 (5.3%) subject who received placebo. All AEs reported as fatigue were mild in intensity and resolved completely.

Deafness
In a Phase 1 study (VER001-1), abnormal audiology findings were noted in 5 subjects who received dalbavancin and in 2 subjects who received placebo. A detailed review of the blinded data by two expert audiologists concluded that the observations were random and probably attributable to poor data collection techniques. The results were inconsistent with ototoxicity for any of the subjects. Subsequent audiologic assessments did not

reveal any evidence of ototoxicity.

Table 8d (Sponsor's Table 10): Adverse Events Occurring in ≥ 2.0% of Dalbavancin Subjects (Phase 1)

	Dalbavancin								
Preferred Term (# and %)	**<500 mg (N = 29)**	**500 – 1000 mg (N = 78)**		**>1000 mg (N = 34)**		**Total (N = 141)**		**Placebo (N = 19)**	
Subjects with at least 1 AE	**21 (72.4)**	**58**	**(74.4)**	**26**	**(76.5)**	**105**	**(74.5)**	**15**	**(78.9)**
Pyrexia	6 (20.7)	9	(11.5)	6	(17.6)	**21**	**(14.9)**	**5**	**(26.3)**
Headache	7 (24.1)	9	(11.5)	2	(5.9)	**18**	**(12.8)**	**4**	**(21.1)**
Upper respiratory tract Infection	2 (6.9)	8	(10.3)	3	(8.8)	**13**	**(9.2)**	**1**	**(5.3)**
Back pain	2 (6.9)	6	(7.7)	1	(2.9)	**9**	**(6.4)**	**1**	**(5.3)**
Nausea	4 (13.8)	4	(5.1)	1	(2.9)	**9**	**(6.4)**		**0**
Pharyngolaryngeal pain	2 (6.9)	5	(6.4)	2	(5.9)	**9**	**(6.4)**		**0**
Diarrhea	1 (3.4)	1	(1.3)	5	(14.7)	**7**	**(5.0)**	**1**	**(5.3)**
Cough	1 (3.4)	6	(7.7)		0	**7**	**(5.0)**		**0**
Fatigue	0	1	(1.3)	5	(14.7)	**6**	**(4.3)**	**1**	**(5.3)**
Nasal congestion	2 (6.9)	4	(5.1)		0	**6**	**(4.3)**	**1**	**(5.3)**
Deafness	5 (17.2)		0		0	**5**	**(3.5)**	**2**	**(10.5)**
ALT increased	0	2	(2.6)	2	(5.9)	**4**	**(2.8)**	**2**	**(10.5)**
Dizziness	0	4	(5.1)		0	**4**	**(2.8)**		**0**
Dyspepsia	1 (3.4)	2	(2.6)	1	(2.9)	**4**	**(2.8)**		**0**
Infusion site pain	0	4	(5.1)		0	**4**	**(2.8)**		**0**
Urinary tract infection	0	2	(2.6)	2	(5.9)	**4**	**(2.8)**		**0**
Vomiting	1 (3.4)	3	(3.8)		0	**4**	**(2.8)**		**0**
AST increased	0	1	(1.3)	2	(5.9)	**3**	**(2.1)**	**2**	**(10.5)**
Hyperglycemia	1 (3.4)	2	(2.6)		0	**3**	**(2.1)**	**1**	**(5.3)**
Hypoglycemia	2 (6.9)		0	1	(2.9)	**3**	**(2.1)**	**1**	**(5.3)**
Constipation	0	3	(3.8)		0	**3**	**(2.1)**		**0**
Proteinuria	0	2	(2.6)	1	(2.9)	**3**	**(2.1)**		**0**
Rash	0	1	(1.3)	2	(5.9)	**3**	**(2.1)**		**0**
Tinnitus	0	1	(1.3)	2	(5.9)	**3**	**(2.1)**		**0**

7.1.5.1 Eliciting adverse events data in the development program

According to the sponsor, "…in all studies, AEs were elicited from the subjects in response to a question about the subject's general health since the last visit, were observed during the examination of the subject, or were spontaneously reported by the subject." In addition, if a patient had a pre-existing condition, "... it was reported as an AE if the frequency increased or if the intensity or character of the condition worsened during study treatment." AE information thus gathered by the investigator was documented, 1) in the CRF, 2) in the data set or, 3) as narratives in the sponsor's integrated safety summary report. Thus, the sources of AE information included:

1. Patient's subjective self-report: The AEs reported as mild to the investigator can not objectively be verified, e.g. nausea or mild abdominal pain.

2. Investigator's open-ended questions with varying degrees of specification.

3. Structured questioning by an investigator (or the investigator's assistant), guided by pre-designed checklist of questions (as in the CRF) customized to the context of the study patients (e.g. type of visit or the nature of patient's disease or AE).

4. By the Investigator's visual impressions of a lesion or the findings of physical evidence of an AE (e.g. rash or swelling of a body part), that represents an AE.

5. Substitution of the investigator's best judgment where information being presented or documented was unclear.

6. Investigator's causality assessment of the AE to the drug received by the patient.

MO's Comments: *The frequency with which patients were assessed varied with the severity of an AE. For non-serious or non-emergency AEs, patients were evaluated during scheduled visits, per protocol. Some AEs necessitated re- hospitalization or extension of hospitalization. It seemed that, for the most part, the situation dictated the decision made. The information obtained from observed physical signs and symptoms were probably the most reliable. Not all AEs could be thus evaluated. There were inherent, perhaps unavoidable, weaknesses in the methods of eliciting information. For example, self-reported AEs could have been minimized by some patients or exaggerated by others according to individual temperament, or even muted if the individual was stoic. While there is no perfect way to perform these tasks, at some level, there is an assumption that the investigators and sponsors have given their best efforts to preserve the integrity of the results submitted for analyses.*

7.1.5.2.1 Appropriateness of adverse event categorization and preferred terms

Overall, the sponsor appears to have provided mostly adequate AE information in preferred terms translated from patient self-reported verbatim terms. This was evident in assembling the adverse events information leading to dropouts or other changes in treatment as well as to serious adverse events. The sponsor presented verbatim terms by MedDRA preferred term. Nevertheless, there were some problems and the method had its shortcomings, as in these examples:

1. According to the sponsor, "MedDRA Version 7.0 was used for recoding all AE terms from the individual Phase 1 studies into the Phase 1 integrated database. Therefore, AE preferred terms may differ slightly from those reported in the individual Phase 1 studies, which used older versions of MedDRA for coding." In addition, "For the Phase 2/3 integrated database, the original AE mapping from the individual studies was used. MedDRA Version 4.1 was used for Study 4. MedDRA Version 5.0 was used for Study 5. MedDRA Version 6.0 was used for Studies 8, 9, and 16. COSTART and older MedDRA yield ample discretion to the AE classifier to choose the term that best reflects the verbatim term reported by the investigator. The true meaning of certain events may be diluted or not captured.

2. Certain terms were used that were close in meaning, e.g. “diarrhea” and “loose stools”. This practice makes the reviewer unclear about the difference and to wonder if the 2 AEs were indeed the same qualitative event. The potential effect on data analysis is that a significant number of AEs (if the 2 groups of subjects are added up) could be reduced to two insignificant AEs (in terms of numbers). But, sometimes it may not make any difference. It just so happens that it does not make any difference by the reviewer’s verification of the dalbavancin-treated patients in this submission.

3. In general, non-specific terms potentially allow sponsors to manage unfavorable information to their advantage if they so choose, although there has been no evidence of that in this review. Disease events with the term “NOS” (not otherwise specified), as in *Infection NOS,* or *Adverse Drug Reaction NOS*, do not provide information about the event that might be vital to assessment of causality.

4. The design of the CRF was, in some aspects, restrictive. n some areas, it left no room for additional comments to enlighten the reviewer about an AE being reported. This hindered the reviewer in doing independent assessment of the event and its relationship to study drug.

7.1.5.3 Incidence of common adverse events

The incidence of common adverse events was obtained by combining the controlled studies of Phases 2 and 3 and obtaining the most frequent AEs as shown in table 8e below. It is the sponsor’s table of their Phases 2/3 integrated database showing the overall most common AEs presented in preferred terms.

The 3 most commonly reported AEs for both treatment groups were nausea, diarrhea, and headache; each of these events was reported less frequently in dalbavancin-treated patients than in comparator-treated patients.

There is a higher incidence of nausea among the patients who received longer duration of therapy (2 doses of dalbavancin and 14 days of the comparator) than those who received shorter duration of therapy (1 dose of dalbavancin and 7 days of the comparator treatment). The frequency was higher in the comparator arm even when the subgroups are compared, i.e. 4.5% (1 dose of dalbavancin treatment) versus 6.8% (7 days of the comparator treatment), or 7.1% (2 doses of dalbavancin treatment) versus 8.8% (14 days of the comparator treatment). Diarrhea and headache did not necessarily fit that pattern (refer to table 8e).

7.1.5.4 Common Adverse Event Tables

Table 8e (Source: ISS Sponsor's Table 13)
The overall most common AEs occurring in ≥ 2% patients in Phases 2/3 integrated Database

	Dalbavancin			Comparator		
Preferred Term	1 Dose (N = 419)	2 Doses (N = 707)	Total (N= 1126)	7 Days (N = 176)	14 Days (N = 397)	Total (N = 573)
Patients with at least 1 AE	**169 (40.3)**	**416 (58.8)**	**585(52.0)**	**73 (41.5)**	**253 (63.7)**	**326 (56.9)**
Nausea	19 (4.5)	50 (7.1)	**69 (6.1)**	12 (6.8)	35 (8.8)	**47 (8.2)**
Diarrhea NOS	24 (5.7)	39 (5.5)	**63 (5.6)**	8 (4.5)	31 (7.8)	**39 (6.8)**
Headache	13 (3.1)	41 (5.8)	**54 (4.8)**	5 (2.8)	28 (7.1)	**33 (5.8)**
Constipation	6 (1.4)	34 (4.8)	**40 (3.6)**	2 (1.1)	17 (4.3)	**19 (3.3)**
Vomiting NOS	10 (2.4)	30 (4.2)	**40 (3.6)**	6 (3.4)	20 (5.0)	**26 (4.5)**
Urinary tract infection NOS	5 (1.2)	29 (4.1)	**34 (3.0)**	1 (0.6)	11 (2.8)	**12 (2.1)**
Anemia NOS	8 (1.9)	23 (3.3)	**31 (2.8)**	2 (1.1)	10 (2.5)	**12 (2.1)**
Rash NOS	9 (2.1)	20 (2.8)	**29 (2.6)**	4 (2.3)	9 (2.3)	**13 (2.3)**
Pruritus	9 (2.1)	16 (2.3)	**25 (2.2)**	4 (2.3)	10 (2.5)	**14 (2.4)**
Insomnia	4 (1.0)	19 (2.7)	**23 (2.0)**	4 (2.3)	22 (5.5)	**26 (4.5)**
Hyperglycemia NOS	3 (0.7)	18 (2.5)	**21 (1.9)**	1 (0.6)	11 (2.8)	**12 (2.1)**
Abdominal pain NOS	3 (0.7)	17 (2.4)	**20 (1.8)**	4 (2.3)	5 (1.3)	**9 (1.6)**
Blood lactate dehydrogenase increased	6 (1.4)	14 (2.0)	**20 (1.8)**	0	12 (3.0)	**12 (2.1)**
Dyspepsia	4 (1.0)	16 (2.3)	**20 (1.8)**	2 (1.1)	4 (1.0)	**6 (1.0)**
Gamma-glutamyl-transferase increased	4 (1.0)	16 (2.3)	**20 (1.8)**	1 (0.6)	12 (3.0)	**13 (2.3)**
Hypoglycemia NOS	2 (0.5)	15 (2.1)	**17 (1.5)**	2 (1.1)	9 (2.3)	**11 (1.9)**
Pyrexia	4 (1.0)	13 (1.8)	**17 (1.5)**	2 (1.1)	11 (2.8)	**13 (2.3)**
Fatigue	5 (1.2)	8 (1.1)	**13 (1.2)**	4 (2.3)	9 (2.3)	**13 (2.3)**
Back pain	0	12 (1.7)	**12 (1.1)**	0	8 (2.0)	**8 (1.4)**
ALT increased	2 (0.5)	9 (1.3)	**11 (1.0)**	3 (1.7)	9 (2.3)	**12 (2.1)**
AST increased	2 (0.5)	4 (0.6)	**6 (0.5)**	4 (2.3)	3 (0.8)	**7 (1.2)**
Loose stools	1 (0.2)	5 (0.7)	**6 (0.5)**	1 (0.6)	13 (3.3)	**14 2.4)**

Degree of Severity of Common AEs

As shown on table 8f, the intensity of nausea was reported mild in 50/69 (72.5%) dalbavancin-treated patients, moderate in 18/60 (26.1%) patients, and severe in 1/60 (1.4%) patient. Of the 47 comparator-treated patients who reported nausea, it was considered mild in 31/47 (66.0%) patients, moderate in 16/47 (34.0%) patients.

Of the 63 dalbavancin-treated patients who reported diarrhea, the intensity was considered mild in 49/63 (77.8%) patients, moderate in 12/63 (19.0%) patients, and severe in 2/63 (3.2%) patients. Diarrhea in the comparator-treated patients was reported as mild in 32 /39 (82.1%) patients, and moderate in 7/39 (17.9%) patients.

Of the 54 dalbavancin-treated patients who reported headache, the intensity was considered mild in 35/54 (64.8%) patients, moderate in 15/54 (27.8%), and severe in 4/54 (7.4%). Among the 33 comparator-treated patients with headache, the headache was of mild intensity in 17/33 (51.5%) patients, of moderate intensity in 15/33 (45.5%) patients, and of severe intensity in 1/33 (3.0%) patient.

Table 8f Number (%) of Common AEs by degree of severity

AE	Dalbavancin	Comparator
Nausea	**N= 69**	**N= 47**
Mild	50 (72.5)	31 (66.0)
Moderate	18 (26.1)	16 (34.0)
Severe	1 (1.4)	-
Diarrhea	**N= 63**	**N= 39**
Mild	49 (77.8)	32 (82.1)
Moderate	12 (19.0)	7 (17.9)
Severe	2 (3.2)	-
Headache	**N= 54**	**N= 33**
Mild	35(64.8)	17 (51.5)
Moderate	15 (27.8)	15(45.5)
Severe	4 (7.4)	1 (3.0)

7.1.5.5 Identifying common and drug-related adverse events

Treatment-Related Adverse Events

Treatment-related AEs that were considered as possibly or probably related to study treatment by the investigator, or AEs for which the relationship to study medication was missing or unknown were classified as treatment-related AEs.
Gastrointestinal disorders were the most commonly reported treatment-related AEs. Eighty-nine (7.9%) dalbavancin-treated patients in the integrated Phase 2/3 database had at least one such AE compared to 59 (10.3%) comparator-treated patients.

Diarrhea was the most commonly reported treatment-related AE for both dalbavancin- and comparator-treated patients. Treatment-related AEs occurring in ≥ 2% of subjects in any treatment arm are presented in table 8g below.

There was no treatment-related AE categorized as "very common" (≥ 10%) in both dalbavancin-treated and comparator-treated patients.
The rates of **"common"** AEs (≥ 1% to <10%) in the dalbavancin-treated patients were reported thus: **diarrhea** (3%), and **nausea** (2.8%). Others not listed in table 8g include increased gamma-glutamyl-transferase (1.4%), rash (1.4%), vomiting (1.2%), increased blood lactate dehydrogenase (1.2%), and headache (1.2%).

All other treatment-related AEs were categorized as "uncommon" if occurring in ≥ 0.1% to < 1% in frequency.

For comparator-treated patients in the Phase 2/3 studies, **"common"** treatment-related AEs were as follows: diarrhea (3.7%), nausea (3.5%), and increased AST (1.0%). Others not in table 8 g include increased gamma-glutamyl-transferase (1.4%), headache (1.4%), loose stools (1.4%), thrombocytopenia (1.4%), increased blood lactate dehydrogenase (1.2%), pruritus (1.2%), fungal vaginosis (1.2%), oral candidiasis (1.2%), rash (1.0%), vomiting (1.0%), increased AST (1.0%), and flushing (1.0%).

Table 8g:
Sponsor's Table 14: Treatment-Related Adverse Events Occurring in ≥2% of Patients in Phase 2/3 Integrated Database

	Dalbavancin			Comparator		
Preferred Term :	**1 Dose (N = 419)**	**2 Doses (N = 707)**	**Total (N = 1126)**	**7 Days (N = 176)**	**14 Days (N = 397)**	**Total (N = 573)**
Patients with at least 1 treatment-related AE: n (%)	**62 (14.8)**	**186 (26.3)**	**248 (22.0)**	**33 (18.8)**	**124 (31.2)**	**157 (27.4)**
Diarrhea NOS	14 (3.3)	20 (2.8)	**34 (3.0)**	3 (1.7)	18 (4.5)	**21 (3.7)**
Nausea	9 (2.1)	23 (3.3)	**32 (2.8)**	6 (3.4)	14 (3.5)	**20 (3.5)**
AST increased	2 (0.5)	3 (0.4)	**5 (0.4)**	4 (2.3)	2 (0.5)	**6 (1.0)**
Loose stools	0	4 (0.6)	**4 (0.4)**	0	8 (2.0)	**8 1.4)**

Patients are counted only once at each level of summarization. AEs in decreasing frequency of preferred term for the total dalbavancin arm.

Duration of the Overall Treatment-related AEs

Duration of all AEs (with available start and stop dates), as well as for the 3 most commonly reported AEs discussed above, are shown in the 2nd, 3rd and 4th blocks in table 8h.
In the first block of table 8 h, a total of 507 (45.0%) dalbavancin-treated patients in Phases 2 and 3 studies and 293 (51.1%) comparator-treated patients had at least 1 AE with available start and stop dates for calculation of AE duration. A total of 409 AEs reported by 212 (18.8%) dalbavancin-treated patients and 245 AEs reported by 133 (23.2%) comparator-treated patients were ongoing at the end of the study; these events were not included in the calculation of AE duration. The median AE duration for dalbavancin-treated patients was 3 days (1 day shorter than comparator-treated patients), and ranged from 1 to 197 days. The mean AE duration was similar between treatment groups.

Duration of the 3 most Common Treatment-related AEs

Durations of the commonly reported AEs of nausea and headache were numerically similar between dalbavancin- and comparator-treated patients (see table 8h). The median duration of **nausea** was 2.0 days for both dalbavancin- and comparator-treated patients, and the median duration of **headache** was 1.0 day for both dalbavancin- and comparator-treated patients. For **diarrhea**, however, the median duration was 2 days shorter for patients treated with dalbavancin, with a median duration of 2.0 days for dalbavancin-treated patients compared with 4.0 days for comparator-treated patients.

Table 8h (modified Sponsor's Table 16): Duration of the Overall Treatment-related AEs

	Dalbavancin			Comparator		
	1 Dose (N = 419)	**2 Doses (N = 707)**	**Total (N = 1126)**	**7 Days (N = 176)**	**14 Days (N = 397)**	**Total (N = 573)**
Patients with at least 1 AE with available start/stop dates	**135 (32.2)**	**372 (52.6)**	**507 (45.0)**	**60 (34.1)**	**2 33 (58.7)**	**293 (51.1)**
AE duration (days)						
Number of events	322	1042	**1364**	146	661	**807**
Mean (SD)	6.0 (8.03)	7.8 (12.02)	**7.4 (11.23)**	6.4 8.30)	7.8 (9.21)	**7.6 (9.06)**
Median	3.0	4.0	**3.0**	3.0	4.0	**4.0**
Minimum Maximum	1 80	1 197	**1 – 197**	1 45	1 84	**1 – 84**
Patients who reported nausea with available start/stop dates	**19 (4.5)**	**44 (6.2)**	**63 (5.6)**	**8 (4.5)**	**34 (8.6)**	**42 (7.3)**
AE duration (days)						
Number of events	19	47	**66**	8	37	**45**
Mean (SD)	2.4 (2.57)	3.8 (4.4)	**3.4 (4.03)**	6.0 (5.3)	3.5 (3.8)	**4.0 (4.13)**
Median	1.0	2.0	**2.0**	4.0	2.0	**2.0**
Minimum Maximum	1 10	1 21	**1 – 21**	2 16	1 15	**1 – 16**
Patients who reported diarrhea with available start/stop dates	**20 (4.8)**	**37 (5.2)**	**57 (5.1)**	**6 (3.4)**	**27 (6.8)**	**33 (5.8)**
AE duration (days)						
Number of events	20	39	**59**	6	27	**33**
Mean (SD)	4.6 (4.95)	3.4 (3.88)	**3.8 (4.27)**	2.2 (1.2)	7.3 (6.61)	**6.3 (6.30)**
Median	2.5	2.0	**2.0**	2.0	5.0	**4.0**
Minimum Maximum	1 18	1 21	**1 – 21**	1 4	1 27	**1 – 27**
Patients who reported headache with available start/stop dates	**12 (2.9)**	**39 (5.5)**	**51 (4.5)**	**5 (2.8)**	**28 (7.1)**	**33 (5.8)**
AE duration (days)						
Number of events	14	41	**55**	5	30	**35**
Mean (SD)	2.2 (3.70)	3.0 (3.66)	**2.8 (3.66)**	1.6 (0.9)	3.6 (5.66)	**3.3 (5.28)**
Median	1.0	1.0	**1.0**	1.0	1.0	**1.0**
Minimum Maximum	1 15	1 14	**1 – 15**	1 3	1 27	**1 – 27**

Duration was calculated as AE stop date minus AE start date, plus 1. For each patient, only AEs with available start and stop dates were included in the computation of average duration. The average AE duration for each patient is summarized in this table.

The overall most common AEs in Phase 1 subjects

Table 8i shows the most frequent AEs in the Phase I integrated database. The two most common are **pyrexia** (i.e., temperature >38.1°C) and **headache**. Pyrexia was reported by 21 (14.9%) dalbavancin-treated subjects compared to 5 (26.3%) reported by placebo-treated subjects. Headache was reported by 18 (12.8%) dalbavancin-treated subjects compared to 4 (21.1%) placebo-treated subjects.

Pyrexia was mild for 25 of the 26 subjects; 1 subject who received 350 mg dalbavancin had pyrexia of moderate intensity. All but 1 case of headache were mild; 1 subject who received 1000 mg dalbavancin had a headache of moderate intensity.

Table 8i (Sponsor's table 10): Adverse Events Occurring in ≥ 2.0 % of Dalbavancin -Treated Subjects [Phase 1 Integrated Database]

	Dalbavancin							
Preferred Term [# (%) of Subjects]	**<500 mg (N = 29)**	**500 – 1000 mg (N = 78)**	**>1000 mg (N = 34)**	**Total (N = 141)**		**Placebo (N = 19)**	
Subjects with at least 1 AE	**21 (72.4)**	**58 (74.4)**	**26 (76.5)**	**105**	**(74.5)**	**15**	**(78.9)**
Pyrexia	6 (20.7)	9 (11.5)	6 (17.6)	**21**	**(14.9)**	**5**	**(26.3)**
Headache	7 (24.1)	9 (11.5)	2 (5.9)	**18**	**(12.8)**	**4**	**(21.1)**
Upper respiratory tract Infection	2 (6.9)	8 (10.3)	3 (8.8)	**13**	**(9.2)**	**1**	**(5.3)**
Back pain	2 (6.9)	6 (7.7)	1 (2.9)	**9**	**(6.4)**	**1**	**(5.3)**
Nausea	4 (13.8)	4 (5.1)	1 (2.9)	**9**	**(6.4)**		**0**
Pharyngolaryngeal pain	2 (6.9)	5 (6.4)	2 (5.9)	**9**	**(6.4)**		**0**
Diarrhea	1 (3.4)	1 (1.3)	5 (14.7)	**7**	**(5.0)**	**1**	**(5.3)**
Cough	1 (3.4)	6 (7.7)	0	**7**	**(5.0)**		**0**
Fatigue	0	1 (1.3)	5 (14.7)	**6**	**(4.3)**	**1**	**(5.3)**
Nasal congestion	2 (6.9)	4 (5.1)	0	**6**	**(4.3)**	**1**	**(5.3)**
Deafness	5 (17.2)	0	0	**5**	**(3.5)**	**2**	**(10.5)**
ALT increased	0	2 (2.6)	2 (5.9)	**4**	**(2.8)**	**2**	**(10.5)**
Dizziness	0	4 (5.1)	0	**4**	**(2.8)**		**0**
Dyspepsia	1 (3.4)	2 (2.6)	1 (2.9)	**4**	**(2.8)**		**0**
Infusion site pain	0	4 (5.1)	0	**4**	**(2.8)**		**0**
Urinary tract infection	0	2 (2.6)	2 (5.9)	**4**	**(2.8)**		**0**
Vomiting	1 (3.4)	3 (3.8)	0	**4**	**(2.8)**		**0**
AST increased	0	1 (1.3)	2 (5.9)	**3**	**(2.1)**	**2**	**(10.5)**
Hyperglycemia	1 (3.4)	2 (2.6)	0	**3**	**(2.1)**	**1**	**(5.3)**
Hypoglycemia	2 (6.9)	0	1 (2.9)	**3**	**(2.1)**	**1**	**(5.3)**
Constipation	0	3 (3.8)	0	**3**	**(2.1)**		**0**
Proteinuria	0	2 (2.6)	1 (2.9)	**3**	**(2.1)**		**0**
Rash	0	1 (1.3)	2 (5.9)	**3**	**(2.1)**		**0**
Tinnitus	0	1 (1.3)	2 (5.9)	**3**	**(2.1)**		

Treatment-Related Adverse Events Occurring in ≥ 2. 0 % of subjects in Phase 1

Pyrexia and headache were also the most reported treatment-related AEs in Phase 1 studies (table 8j). Five subjects in the dalbavancin (<500 mg group) and 2 in the placebo group, had an AE of deafness, the preferred term used by the investigator to describe asymptomatic audiometry findings. In a detailed review of the blinded data, two expert audiologists concluded that the changes observed were random and probably attributable to poor data collection techniques and not true hearing loss.

Table 8j (Sponsor's Table 11): Treatment-Related Adverse Events Occurring in ≥ 2.0 % of Dalbavancin-treated Subjects in Phase 1 [Number (%) of Subjects]

	Dalbavancin							
Preferred Term	<500 mg (N = 29)	500 – 1000 mg (N = 78)		>1000 mg (N = 34)		Total (N = 141)		Placebo (N = 19)	
Subjects with at Least 1 treatment-related AE	**13 (44.8)**	**24**	**(30.8)**	**13**	**(38.2)**	**50**	**(35.5)**	**11**	**(57.9)**
Pyrexia	5 (17.2)	7	(9.0)	2	(5.9)	**14**	**(9.9)**	**4**	**(21.1)**
Headache	3 (10.3)	2	(2.6)	1	(2.9)	**6**	**(4.3)**	**1**	**(5.3)**
Deafness	5 (17.2)		0		0	**5**	**(3.5)**	**2**	**(10.5)**
Infusion site pain	0	4	(5.1)		0	**4**	**(2.8)**		**0**
Diarrhea	1 (3.4)		0	2	(5.9)	**3**	**(2.1)**	**1**	**(5.3)**
Fatigue	0		0	3	(8.8)	**3**	**(2.1)**	**1**	**(5.3)**
Nausea	1 (3.4)	1	(1.3)	1	(2.9)	**3**	**(2.1)**		**0**

Treatment-related AEs were defined as those reported as possibly or probably related to study treatment by the investigator. Subjects are counted only once at each level of summarization.

7.1.5.6 Additional analyses and explorations

No unexplored or other safety issues warranting additional analyses in this section

7.1.6 Less Common Adverse Events

The less common AEs (also classified by the sponsors as "uncommon" AEs) include AEs ≥ 0.1% but < 1% in frequency. In this submission, they are listed in decreasing order of frequency. As they affect dalbavancin-treated patients, the AEs are in 25 such tables submitted by the sponsor (for Phase 2/3 integrated database), and in 33 tables if the comparators are used. Table 8k is the upper segment and table 8L the lower segment of these less common 25 AE tables. There are 23 additional tables in between these two (top and bottom) segments or tables.

Table 8k (Modified sponsors table): Less Common Adverse Events (Phases 2 and 3)

AE Preferred Term	Dalbavancin 1 dose (N=419)	Dalbavancin 2 doses (N=707)	Total Dalbavancin (N=1126)	Comparator 7 days (N=176)	Comparator 14 days (N=397)	Total Comparator (N=573)
APPETITE DECREASED NOS	0	6 (0.8)	6 (0.5)	0	5 (1.3)	5 (0.9)
BLOOD GLUCOSE INCREASED	1 (0.2)	5 (0.7)	6 (0.5)	1 (0.6)	3 (0.8)	4 (0.7)
PLATELET COUNT INCREASED	0	6 (0.8)	6 (0.5)	1 (0.6)	3 (0.8)	4 (0.7)
PHLEBITIS NOS	2 (0.5)	4 (0.6)	6 (0.5)	0	3 (0.8)	3 (0.5)
ASTHENIA	3 (0.7)	3 (0.4)	6 (0.5)	1 (0.6)	1 (0.3)	2 (0.3)
TRANSAMINASES INCREASED	0	6 (0.8)	6 (0.5)	0	2 (0.5)	2 (0.3)
DYSURIA	1 (0.2)	5 (0.7)	6 (0.5)	0	1 (0.3)	1 (0.2)
INFLUENZA LIKE ILLNESS	0	6 (0.8)	6 (0.5)	0	1 (0.3)	1 (0.2)
SKIN AND SUBCUTANEOUS TISSUE ABSCESS NOS	2 (0.5)	4 (0.6)	6 (0.5)	1 (0.6)	0	1 (0.2)
AGITATION	1 (0.2)	5 (0.7)	6 (0.5)	0	0	0
LETHARGY	0	6 (0.8)	6 (0.5)	0	0	0
WHITE BLOOD CELL COUNT INCREASED	2 (0.5)	4 (0.6)	6 (0.5)	0	0	0
ORAL CANDIDIASIS	0	5 (0.7)	5 (0.4)	1 (0.6)	6 (1.5)	7 (1.2)
HAEMATURIA	2 (0.5)	3 (0.4)	5 (0.4)	2 (1.1)	4 (1.0)	6 (1.0)
EOSINOPHILIA	0	5 (0.7)	5 (0.4)	0	5 (1.3)	5 (0.9)
ERYTHEMA	1 (0.2)	4 (0.6)	5 (0.4)	1 (0.6)	4 (1.0)	5 (0.9)
RIGORS	2 (0.5)	3 (0.4)	5 (0.4)	1 (0.6)	4 (1.0)	5 (0.9)
GENITAL PRURITUS FEMALE	0	5 (0.7)	5 (0.4)	0	4 (1.0)	4 (0.7)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

Table 8L (Modified sponsors table): Less Common Adverse Events (Phase 2 and 3) -continued

AE Preferred Term	Dalbavancin 1 dose (N=419)	Dalbavancin 2 doses (N=707)	Total Dalbavancin (N=1126)	Comparator 7 days (N=176)	Comparator 14 days (N=397)	Total Comparator (N=573)
TOE AMPUTATION	0	1 (0.1)	1 (0.1)	0	0	0
TOOTH ABSCESS	0	1 (0.1)	1 (0.1)	0	0	0
TRANSFUSION REACTION	0	1 (0.1)	1 (0.1)	0	0	0
URETHRAL STRICTURE	0	1 (0.1)	1 (0.1)	0	0	0
URINE ABNORMAL NOS	1 (0.2)	0	1 (0.1)	0	0	0
VAGINITIS	0	1 (0.1)	1 (0.1)	0	0	0
VENOUS ULCER NOS	0	1 (0.1)	1 (0.1)	0	0	0
VENTRICULAR TACHYCARDIA	0	1 (0.1)	1 (0.1)	0	0	0
VISION BLURRED	1 (0.2)	0	1 (0.1)	0	0	0
VULVOVAGINAL DISCOMFORT	0	1 (0.1)	1 (0.1)	0	0	0
WEIGHT INCREASED	0	1 (0.1)	1 (0.1)	0	0	0
WOUND CLOSURE NEC	1 (0.2)	0	1 (0.1)	0	0	0
WOUND DEBRIDEMENT	0	1 (0.1)	1 (0.1)	0	0	0
WOUND DEHISCENCE	0	1 (0.1)	1 (0.1)	0	0	0
WOUND DRAINAGE	1 (0.2)	0	1 (0.1)	0	0	0
WOUND HAEMORRHAGE	0	1 (0.1)	1 (0.1)	0	0	0
INFUSION SITE ERYTHEMA	0	0	0	0	5 (1.3)	5 (0.9)
FOOT ULCER	0	0	0	0	3 (0.8)	3 (0.5)
HYPOALBUMINAEMIA	0	0	0	0	3 (0.8)	3 (0.5)
CATHETER RELATED INFECTION	0	0	0	0	2 (0.5)	2 (0.3)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing

Content of submission in the evaluation of laboratory values

- ❖ Vicuron Pharmaceuticals Inc. submitted laboratory values of subjects/patients in hematology, chemistry, and urinalysis.

Methods employed to identify safety signals

- ❖ Potentially clinically significant (PCS) trends were compared across study arms for any safety signals. Abnormalities considered outliers were sought for evaluation. Dose-related adverse event trends were also evaluated within and across study arms.

Laboratory values examined

Hematology Parameters

- o These included white blood cells (WBC), hemoglobin (Hb)/ percentage hematocrit (Hct), and platelets (Plt). Trends were also evaluated in WBC differential profiles: neutrophils, lymphocytes, eosinophils, basophils, and monocytes.

Chemistry Parameters

- o Chemistry parameters provided were evaluated for potential safety signals in hepatobiliary and renal systems.
- o Potential abnormalities in Blood Urea Nitrogen (BUN), creatinine, electrolytes were explored across study arms, as were outlier values to ascertain uncommon and idiosyncratic abnormalities.
- o Potential abnormalities in hepatobiliary system were determined by elevations of liver aminotransferases, i.e. serum Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST); Alkaline Phosphatase (ALP), Gamma Glutamyl Transpeptidase (GGT), Lactic Dehydrogenase (LDH), and bilirubin. These were examined for abnormal trends across study arms. Outliers, and the severity of their parameters, were evaluated. Shifts in laboratory values from baseline over the course of studies and the relationship to study drugs were determined.
- o Urinalysis values were examined for genito-urinary abnormalities.

Schedule for Clinical Laboratory Testing

- o Laboratory values were obtained at baseline (i.e. within 24 hours before the first dose of the drug), on treatment, at the end of therapy (EOT), at test of cure (TOC) and during late follow up period.

Some unscheduled tests were done between these time lines necessitated by an event (e.g. hospitalization for an adverse event) or by a need to follow up on an abnormal test result. Laboratory values for each subject/patient were assessed for any potentially clinically significant changes in clinical laboratory parameters by the investigator and assistants.

While many patients who had AEs were followed until their values normalized, a smaller number of patients with abnormal laboratory values were lost to follow up. No patient that experienced a dalbavancin treatment-related AE was re-challenged, to the reviewer's knowledge, for reproducibility, even with the milder AEs.
Some laboratory abnormalities that developed in some patients during the study were followed for as long as a year or longer. A patient in study 9 (09-057-001) with ALT and AST elevations was followed until Day 382 post dalbavancin treatment.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The most reliable data are from blinded controlled trials. Consistent with the approach from the outset, blinded comparative controlled studies were combined. Unblinded (open-label) comparative studies were also combined and analyzed for safety signals, as were Phase 1 studies.
The analyses submitted by the sponsor included a comparison between study drug and comparators for laboratory parameters of potential clinical significance. The sponsor specified a normal range for each laboratory parameter as well as levels of deviation from limits of stated normal ranges (upper or lower) to enable detection of these potentially clinically significant laboratory abnormalities.

Serum Chemistry

The sponsor used the following criteria to identify patients with potentially clinically significant chemistry abnormalities:

(1) The number [and percentage] of patients whose laboratory values were above or below a laboratory-defined or sponsor-defined clinically significant range.

(2) The number (%) of subjects whose laboratory values had shifted (increased or decreased) from baseline by a sponsor-defined potentially clinically significant change (PCSC) at each post-baseline time point.

(3) Number (%) of patients with both PCS and PCSC laboratory tests at each post-baseline time point.

(4) Number (%) of patients with prospectively specified abnormalities in a given tier beyond Upper Limit of Normal (ULN) e.g. ALT or AST(>ULN- 3×ULN, >3×ULN-

>5×ULN, >10×ULN, and >20 × ULN) were given. These were also specified for AST, alkaline phosphatase or total bilirubin (>1.5×ULN) at each time point. [See table 9aa, below].

Table 9aa (Sponsor's Table 27)
Sponsor's Criteria for Identifying PCS and PCSC Laboratory Test Results

	Potentially Clinically Significant Criteria			
Parameter	**Lower Limit (Absolute Values)**	**Fold Decrease From Baseline**	**Upper Limit (Absolute Values)**	**Fold Increase From Baseline**
Hematology				
Hemoglobin	0.8 × LLN	0.25	1.3 × ULN	1.4
Haematocrit	0.8 × LLN	0.25	1.3 × ULN	1.4
Leukocytes	0.5 × LLN	0.75	2.0 × ULN	2.0
Neutrophils	0.5 × LLN	0.75	2.2 × ULN	2.0
Lymphocytes	0.2 × LLN	0.75	2.2× ULN	2.0
Eosinophils	NA	NA	4.0 × ULN[a]	4.0[a]
Platelets	0.6 × LLN	0.4	2.0× ULN	2.0
Chemistry				
Magnesium	0.4 × LLN	0.6	4.0 × ULN	4.0
Bicarbonate	0.8 × LLN	0.5	1.3 × ULN	1.3
Sodium	0.9 × LLN	0.1	1.1 × ULN	1.1
Potassium	0.85 × LLN	0.15	1.2 × ULN	1.2
Chloride	0.8 × LLN	0.2	1.2 × ULN	1.2
Calcium	0.7 × LLN	0.3	1.3 × ULN	1.3
Alkaline phosphatase	NA	NA	1.5 × ULN	2.0
GGT	NA	NA	1.5 × ULN	2.0
ALT	NA	NA	3.0 × ULN	3.0
AST	NA	NA	3.0 × ULN	3.0
LDH	NA	NA	5.0 × ULN	5.0
Total bilirubin	NA	NA	1.5 × ULN	3.0
Glucose	0.6 × LLN	0.4	3.0 × ULN	3.0
Total protein	0.4 × LLN	0.6	2.0 × ULN	2.0
Albumin	0.4 × LLN	0.6	NA	NA
Creatinine	NA	NA	1.5 × ULN	2.0
Urea nitrogen	NA	NA	3.0 × ULN	3.0
Uric acid	NA	NA	3.0 × ULN	5.0

LLN=lower limit of normal; ULN=upper limit of normal; NA=not applicable; GGT=gamma-glutamyl transferase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDH=lactate dehydrogenase.
[a]PCS criteria for eosinophils also included positive follow-up values when the baseline value was zero

7.1.7.3 Standard analyses and explorations of laboratory data

Review of Hepatobiliary Parameters

- Subjects that met sponsor-defined criteria for hepatobiliary abnormalities are grouped in table 9a according to laboratory value, and in tiers, determined by their deviations from their respective upper limit of normal (ULN).

- ❖ Many of the dalbavancin-treated patients who had hepatobiliary abnormalities during the study had abnormalities present at baseline.
- ❖ A large majority of the patients in both treatment arms with hepatobiliary abnormalities had elevations in ALT and AST that were within >ULN to 3×ULN range compared to the other tiers of hepatobiliary laboratory abnormalities.
- ❖ There were no definitive trends in post-baseline hepatobiliary abnormalities between patients who received 1 dose versus 7 days of treatment and those who received 2 doses versus 14 days of treatment.
- ❖ There were no deaths, discontinuation of study drug or withdrawal from the study due to hepatobiliary abnormalities. One dalbavancin and another patient who was comparator-treated each had cholecystitis reported as an SAE.
- ❖ A subject in Phase 1 with ALT and AST > 20x ULN was lost to follow up and is reviewed under and along with Phase 1 subjects.

Table 9a: Overall Aminotransferase and Bilirubin Abnormalities for Studies 8 and 9

	Dalbavancin (N = 938)						**Comparator (N = 469)**					
By ALT	**1 dose n =344**	**%**	**2 doses n =594**	**%**	**Total N=938**	**%**	**7 days n =153**	**%**	**14days n =316**	**%**	**Total N=469**	**%**
>20xULN	1	0.3	1	0.2	**2**	**0.2**	0	**-**	0	**-**	**0**	**-**
>10xULN - 20xULN	0	-	0	-	**0**	**-**	0	-	0	-	**0**	**-**
>5x-10xULN	3	0.9	2	0.4	**5**	**0.5**	0	-	5	1.5	**5**	**1.1**
>3x-5xULN	5	1.4	14	2.4	**19**	**2.0**	0	-	11	3.5	**11**	**2.3**
>3x-5xULN - ↑ from normal BL	2	0.6	6	1	**8**	**0.9**	0	-	2	0.6	**2**	**0.4**
>3x-5xULN – ↑ from abnormal BL	3	0.9	8	1.6	**11**	**1.2**	0	-	9	2.8	**9**	**1.9**
By AST	**1 dose n =344**	**%**	**2 doses n =594**	**%**	**Total n=938**	**%**	**7 days n =153**	**%**	**14days n =316**	**%**	**Total n=469**	**%**
>20xULN	0	-	1	0.2	**1**	**0.1**	0	-	0	-	**0**	**-**
>10xULN - 20xULN	2	0.6	0	-	**2**	**0.2**	0	-	1	0.3	**1**	**0.2**
>5x-10xULN	2	0.6	1	0.2	**3**	**0.3**	0	-	3	1	**3**	**0.6**
>3x-5xULN = total ↑ from BL	3	0.9	10	1.7	**13**	**1.4**	2	1.3	5	1.6	**7**	**1.5**
>3x-5xULN = ↑ from normal BL	1	0.3	3	0.5	**4**	**0.4**	2	1.3	1	0.3	**4**	**1.3**
By Bili >1.5 x ULN	**1 dose n =344**	**%**	**2 doses n =594**	**%**	**Total n=938**	**%**	**7 days n =153**	**%**	**14days n =316**	**%**	**Total n=469**	**%**
Rise from normal baseline levels	2	0.6	3	0.5	**5**	**0.5**	1	0.7	1	0.3	**2**	**0.4**
Rise from abnormal baseline levels	6	1.7	17	2.9	**23**	**2.5**	4	2.6	6	1.9	**10**	**2.1**
Above two categories combined	8	2.3	20	3.4	**28**	**3.0**	5	3.3	7	2.2	**12**	**2.5**
Clinically significant Alk. Phos ↑	10	2.9	28	4.7	**38**	**4.1**	5	3.3	14	4.4	**19**	**4.1**
Hy's Law Cases	0	-	0	-	0	-	0	-	0	-	0	-

ALT = Alanine Aminotransferase; AST= Aspartate Aminotransferase; Bili = Bilirubin; Alk. Phos = alkaline Phosphatase
BL = Baseline; ↑ = Increase(d).

MO's Comment: *Table 9a was reviewer- designed to get an overall picture of the different tiers of abnormalities among the key enzymes (ALT and AST) and bilirubin*

obtained at the visits with the highest post- baseline abnormal levels and how they compare across study arms. The two ALT (and 1 AST) abnormalities at the >20xULN tier stand out and will be reviewed in greater detail further down in this review. The lower tiers in the table are fairly similar across study arms; there were no significant differences between treatment groups.

7.1.7.3.2 Analyses Focused on Outliers or Shifts from Normal to Abnormal

Tables 9b and 9c (tables resubmitted by the sponsor) show the number of patients with ALT and AST elevations respectively at the different scheduled visits and at different levels of laboratory abnormalities. Of note, the enzyme abnormalities in most patients (whether ALT or AST) lie in the >ULN - 3xULN level. In addition, excluding outliers, the frequencies of most enzyme abnormalities are comparable across study arms.

Tables 9d and 9e (also the sponsor's resubmitted tables) show that Alkaline Phosphatase, ALT and AST transition profiles for dalbavancin-treated patients at the EOT visit. At the EOT visit, 5 (0.7%) patients whose ALT levels were at ULN - 3xULN at baseline had ALT elevations at >3x – 5x ULN. One patient's ALT remained at >3x – 5x ULN from baseline to the EOT visit. At EOT no dalbavancin-treated patient had ALT abnormality at > 5x – 10 x ULN in studies 8 and 9.

Tables 9f and 9g (sponsor's resubmitted tables) show Alkaline Phosphatase, ALT and AST transition profiles for dalbavancin-treated and comparator-treated patients respectively at the TOC visit. Among the dalbavancin-treated patients, 1 (0.1%) patient who had an ALT level < ULN at baseline had ALT elevation > 10 x ULN by the TOC visit; another had an ALT elevation at > 5x – 10x ULN.

In addition, tables containing results of earlier visits were also submitted by the sponsor and are available (but not included in this review).

MO's Comment: *These tables convey information about patients' laboratory values at different time points, including changes (increase or decrease) with subsequent visits. The numbers were small. The CRFs of this small number of patients were scrutinized for additional information surrounding these abnormal values, particularly the possible causal relationship between the study drug and the laboratory abnormality in question. Causal relationship could not be determined with reasonable certainty.*

Table 9b: (Sponsor's redesigned table) Patients With Different Levels of Abnormal ALT Results according to study visits in Studies 8 and 9

Number (%) with abnormal hepatobiliary tests		Dalbavancin 1 dose N	Dalbavancin 1 dose n (%)	Dalbavancin 2 doses N	Dalbavancin 2 doses n (%)	Total Dalbavancin N	Total Dalbavancin n (%)	Comparator 7 days N	Comparator 7 days n (%)	Comparator 14 days N	Comparator 14 days n (%)	Total Comparator N	Total Comparator n (%)
ALT													
>ULN - 3xULN	Baseline	314	40 (12.7)	562	67 (11.9)	876	107 (12.2)	141	15 (10.6)	303	47 (15.5)	444	62 (14.0)
	On-tx	6	1 (16.7)	562	115 (20.5)	568	116 (20.4)	5	1 (20.0)	292	67 (22.9)	297	68 (22.9)
	EOT	266	45 (16.9)	538	72 (13.4)	804	117 (14.6)	128	18 (14.1)	280	61 (21.8)	408	79 (19.4)
	TOC	255	20 (7.8)	524	51 (9.7)	779	71 (9.1)	125	13 (10.4)	271	54 (19.9)	396	67 (16.9)
>3xULN - 5xULN	Baseline	314	1 (0.3)	562	2 (0.4)	876	3 (0.3)	141	0	303	5 (1.7)	444	5 (1.1)
	On-tx	6	0	562	7 (1.2)	568	7 (1.2)	5	0	292	5 (1.7)	297	5 (1.7)
	EOT	266	3 (1.1)	538	3 (0.6)	804	6 (0.7)	128	0	280	2 (0.7)	408	2 (0.5)
	TOC	255	2 (0.8)	524	4 (0.8)	779	6 (0.8)	125	0	271	4 (1.5)	396	4 (1.0)
>5xULN - 10xULN	Baseline	314	0	562	1 (0.2)	876	1 (0.1)	141	0	303	2 (0.7)	444	2 (0.5)
	On-tx	6	0	562	1 (0.2)	568	1 (0.2)	5	0	292	2 (0.7)	297	2 (0.7)
	EOT	266	0	538	0	804	0	128	0	280	3 (1.1)	408	3 (0.7)
	TOC	255	2 (0.8)	524	0	779	2 (0.3)	125	0	271	2 (0.7)	396	2 (0.5)
>10xULN - 20xULN	Baseline	314	0	562	0	876	0	141	0	303	0	444	0
	On-tx	6	0	562	0	568	0	5	0	292	0	297	0
	EOT	266	0	538	0	804	0	128	0	280	0	408	0
	TOC	255	0	524	0	779	0	125	0	271	0	396	0
>20xULN	Baseline	314	0	562	1 (0.2)	876	1 (0.1)	141	0	303	0	444	0
	On-tx	6	0	562	0	568	0	5	0	292	0	297	0
	EOT	266	0	538	0	804	0	128	0	280	0	408	0
	TOC	255	1 (0.4)	524	0	779	1 (0.1)	125	0	271	0	396	0

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization. On-tx (On-treatment) = Day 8. EOT = End of Treatment. TOC = Test of Cure. The number of patients with available laboratory results at a specific time is used in computing percentages.

Table 9c (Sponsor's Table): Patients With Different Levels of Abnormal AST values according to study visits in Studies 8 and 9

Number (%) with abnormal hepatobiliary tests		Dalbavancin 1 dose N	Dalbavancin 1 dose n (%)	Dalbavancin 2 doses N	Dalbavancin 2 doses n (%)	Total Dalbavancin N	Total Dalbavancin n (%)	Comparator 7 days N	Comparator 7 days n (%)	Comparator 14 days N	Comparator 14 days n (%)	Total Comparator N	Total Comparator n (%)
AST													
>ULN - 3xULN	Baseline	315	34 (10.8)	562	76 (13.5)	877	110 (12.5)	142	11 (7.7)	302	51 (16.9)	444	62 (14.0)
	On-tx	6	0	560	96 (17.1)	566	96 (17.0)	5	1 (20.0)	292	54 (18.5)	297	55 (18.5)
	EOT	266	42 (15.8)	540	63 (11.7)	806	105 (13.0)	129	11 (8.5)	283	39 (13.8)	412	50 (12.1)
	TOC	255	20 (7.8)	524	56 (10.7)	779	76 (9.8)	125	13 (10.4)	271	36 (13.3)	396	49 (12.4)
>3xULN - 5xULN	Baseline	315	4 (1.3)	562	2 (0.4)	877	6 (0.7)	142	0	302	4 (1.3)	444	4 (0.9)
	On-tx	6	0	560	8 (1.4)	566	8 (1.4)	5	0	292	2 (0.7)	297	2 (0.7)
	EOT	266	3 (1.1)	540	2 (0.4)	806	5 (0.6)	129	2 (1.6)	283	3 (1.1)	412	5 (1.2)
	TOC	255	2 (0.8)	524	1 (0.2)	779	3 (0.4)	125	0	271	2 (0.7)	396	2 (0.5)
>5xULN - 10xULN	Baseline	315	0	562	1 (0.2)	877	1 (0.1)	142	0	302	3 (1.0)	444	3 (0.7)
	On-tx	6	0	560	1 (0.2)	566	1 (0.2)	5	0	292	2 (0.7)	297	2 (0.7)
	EOT	266	0	540	0	806	0	129	0	283	1 (0.4)	412	1 (0.2)
	TOC	255	2 (0.8)	524	1 (0.2)	779	3 (0.4)	125	0	271	2 (0.7)	396	2 (0.5)
>10xULN - 20xULN	Baseline	315	1 (0.3)	562	0	877	1 (0.1)	142	0	302	0	444	0
	On-tx	6	0	560	0	566	0	5	0	292	0	297	0
	EOT	266	0	540	0	806	0	129	0	283	0	412	0
	TOC	255	1 (0.4)	524	0	779	1 (0.1)	125	0	271	1 (0.4)	396	1 (0.3)
>20xULN	Baseline	315	0	562	1 (0.2)	877	1 (0.1)	142	0	302	0	444	0
	On-tx	6	0	560	0	566	0	5	0	292	0	297	0
	EOT	266	0	540	0	806	0	129	0	283	0	412	0
	TOC	255	0	524	0	779	0	125	0	271	0	396	

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization. On-tx (On-treatment) = Day 8. EOT = End of Treatment. TOC = Test of Cure. The number of patients with available laboratory results at a specific time is used in computing percentages.

Table 9d (Sponsor's Table): Hepatobiliary Transition Profile for Dalbavancin-Treated Patients at The EOT visit

		Total Dalbavancin					
			EOT				
Parameter	**Baseline**	**N[a]**	<ULN N (%)	ULN - 3xULN N (%)	>3x - 5xULN N (%)	>5x - 10xULN N (%)	>10xULN N (%)
Alk Phos	<ULN	688	660 (85.5)	28 (3.6)	0	0	0
	ULN - 3xULN	83	30 (3.9)	53 (6.9)	0	0	0
	>3x - 5xULN	1	0	1 (0.1)	0	0	0
	>5x - 10xULN	0	0	0	0	0	0
	>10xULN	0	0	0	0	0	0
ALT	<ULN	662	599 (79.0)	63 (8.3)	0	0	0
	ULN - 3xULN	92	36 (4.7)	51 (6.7)	5 (0.7)	0	0
	>3x - 5xULN	2	1 (0.1)	0	1 (0.1)	0	0
	>5x - 10xULN	1	0	1 (0.1)	0	0	0
	>10xULN	1	1 (0.1)	0	0	0	0
AST	<ULN	650	594 (78.0)	56 (7.3)	0	0	0
	ULN - 3xULN	104	54 (7.1)	47 (6.2)	3 (0.4)	0	0
	>3x - 5xULN	5	2 (0.3)	1 (0.1)	2 (0.3)	0	0
	>5x - 10xULN	1	0	1 (0.1)	0	0	0
	>10xULN	2	1 (0.1)	1 (0.1)	0	0	0

[a] Number of subjects with both baseline and specified visit evaluation; percentage based on number of subjects with both baseline and visit evaluations.
Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment.
ULN = Upper Limit of Normal. On-treatment = Day 8. EOT = End of Treatment.

Table 9e (Sponsor's Table): Hepatobiliary Transition Profile for comparator-treated patients at The EOT visit

		Total Comparator					
			EOT				
			<ULN	ULN - 3xULN	>3x - 5xULN	>5x - 10xULN	>10xULN
Parameter	**Baseline**	**N[a]**	N (%)	N (%)	N (%)	N (%)	N (%)
Alk Phos	<ULN	345	331 (84.4)	14 (3.6)	0	0	0
	ULN - 3xULN	47	25 (6.4)	22 (5.6)	0	0	0
	>3x - 5xULN	0	0	0	0	0	0
	>5x - 10xULN	0	0	0	0	0	0
	>10xULN	0	0	0	0	0	0
ALT	<ULN	318	281 (73.2)	36 (9.4)	0	1 (0.3)	0
	ULN - 3xULN	60	20 (5.2)	40 (10.4)	0	0	0
	>3x - 5xULN	4	0	3 (0.8)	0	1 (0.3)	0
	>5x - 10xULN	2	0	0	1 (0.3)	1 (0.3)	0
	>10xULN	0	0	0	0	0	0
AST	<ULN	324	303 (77.7)	19 (4.9)	2 (0.5)	0	0
	ULN - 3xULN	60	29 (7.4)	29 (7.4)	1 (0.3)	1 (0.3)	0
	>3x - 5xULN	3	3 (0.8)	0	0	0	0
	>5x - 10xULN	3	1 (0.3)	1 (0.3)	1 (0.3)	0	0
	>10xULN	0	0	0	0	0	0

[a] Number of subjects with both baseline and specified visit evaluation; percentage based on number of subjects with both baseline and visit evaluations.
Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. ULN = Upper Limit of Normal. On-treatment = Day 8. EOT = End of Treatment. TOC = Test of Cure.

Table 9f : Hepatobiliary Transition Profile for Total dalbavancin-treated patients at The TOC visit

		Total Dalbavancin					
			TOC				
			<ULN	ULN - 3xULN	>3x - 5xULN	>5x - 10xULN	>10xULN
Parameter	**Baseline**	**N[a]**	N (%)	N (%)	N (%)	N (%)	N (%)
Alk Phos	<ULN	656	629 (85.1)	26 (3.5)	1 (0.1)	0	0
	ULN - 3xULN	82	41 (5.5)	40 (5.4)	1 (0.1)	0	0
	>3x - 5xULN	1	1 (0.1)	0	0	0	0
	>5x - 10xULN	0	0	0	0	0	0
	>10xULN	0	0	0	0	0	0
ALT	<ULN	635	595 (81.5)	37 (5.1)	1 (0.1)	1 (0.1)	1 (0.1)
	ULN - 3xULN	92	49 (6.7)	37 (5.1)	5 (0.7)	1 (0.1)	0
	>3x - 5xULN	1	1 (0.1)	0	0	0	0
	>5x - 10xULN	1	1 (0.1)	0	0	0	0
	>10xULN	1	1 (0.1)	0	0	0	0
AST	<ULN	629	582 (79.7)	43 (5.9)	1 (0.1)	2 (0.3)	1 (0.1)
	ULN - 3xULN	94	58 (7.9)	34 (4.7)	1 (0.1)	1 (0.1)	0
	>3x - 5xULN	5	3 (0.4)	1 (0.1)	1 (0.1)	0	0
	>5x - 10xULN	1	1 (0.1)	0	0	0	0
	>10xULN	1	1 (0.1)	0	0	0	0

[a] Number of subjects with both baseline and specified visit evaluation; percentage based on number of subjects with both baseline and visit evaluations.
Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment.
ULN = Upper Limit of Normal. On-treatment = Day 8. EOT = End of Treatment. TOC = Test of Cure.

Table 9g: Hepatobiliary Transition Profile for Total Comparator-Treated Patients at The TOC visit

Parameter	Baseline	N[a]	<ULN N (%)	ULN - 3xULN N (%)	>3x - 5xULN N (%)	>5x - 10xULN N (%)	>10xULN N (%)
Alk Phos	<ULN	333	318 (84.4)	15 (4.0)	0	0	0
	ULN - 3xULN	44	23 (6.1)	21 (5.6)	0	0	0
	>3x - 5xULN	0	0	0	0	0	0
	>5x - 10xULN	0	0	0	0	0	0
	>10xULN	0	0	0	0	0	0
ALT	<ULN	308	280 (75.3)	28 (7.5)	0	0	0
	ULN - 3xULN	58	22 (5.9)	35 (9.4)	1 (0.3)	0	0
	>3x - 5xULN	5	0	2 (0.5)	2 (0.5)	1 (0.3)	0
	>5x - 10xULN	1	0	0	0	1 (0.3)	0
	>10xULN	0	0	0	0	0	0
AST	<ULN	315	291 (77.6)	22 (5.9)	0	1 (0.3)	1 (0.3)
	ULN - 3xULN	55	26 (6.9)	26 (6.9)	2 (0.5)	1 (0.3)	0
	>3x - 5xULN	4	3 (0.8)	1 (0.3)	0	0	0
	>5x - 10xULN	1	0	1 (0.3)	0	0	0
	>10xULN	0	0	0	0	0	0

[a] Number of subjects with both baseline and specified visit evaluation; percentage based on number of subjects with both baseline and visit evaluations
Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. ULN = Upper Limit of Normal. On-treatment = Day 8. EOT = End of Treatment. TOC = Test of Cure.

7.1.7.3.3 Marked Outliers and Dropouts for Laboratory Abnormalities

Patients with ALT values >20 x ULN

Two patients in studies 8 and 9 had ALT levels > 20x ULN. One had ALT level > 20x ULN at baseline. His brief narrative (Patient 1 below) and his enzyme transition profile (table 9h) are provided. The narrative for the second patient (Patient 2 below) and his enzyme transition profile (table 9i) are also provided.

Patient 1

Patient # 08066007, a 43-year-old Caucasian male who received 2 doses of dalbavancin, was enrolled with a baseline ALT of 1402 U/L (normal range = 1-60 U/L) and a normal bilirubin level of 11 umol/L (normal range = 0-24 umol/L). The rest of the patient's liver laboratory test transition profile is as shown in table 9h. The subject admitted to a history of chronic Tylenol abuse, according to the CRF, which was the putative cause of his baseline liver enzyme elevations.

Table 9h: Hepatobiliary Laboratory Transition Profile for Patient 08066007

Lab Test	Normal Range	Baseline	Day 8	EOT	TOC
ALT	1 - 60 (U/L)	1402	183	55	37
AST	8 - 40 (U/L)	956	30	33	32
Total Bili	0 – 24 (umol/L)	11	10	10	11
GGT	11 – 63 (U/L)	236	215	188	176
Alk Phos	30 - 130(U/L)	175	121	132	121
LDH	100 - 235(U/L)	495	136	144	194

Patient 2

Sponsor's narrative of 08-206-017
Patient 08-206-017, a 33-year-old Caucasian male who participated in a European study and received 1 dose of dalbavancin, had elevated ALT and AST levels at the TOC visit (Day 27). On Day 27, the patient's ALT was 953 U/L (baseline value was 14 U/L; EOT value on Day 8 was 16 U/L), and his AST was 716 U/L (baseline value was 23 U/L; EOT value on Day 8 was 25 U/L). The abnormalities in this patient's transaminases were reported by the investigator to be the result of alcoholic hepatitis; the investigator confirmed that the patient was drinking heavily on vacation prior to the TOC visit. This event was reported as a mild AE with onset on Day 27 and with subsequent resolution. This was considered by the investigator to be unrelated to study drug. Follow-up conducted on Day 35 showed improving (decreasing) values for ALT and AST; the patient's ALT had decreased to 317 U/L, and his AST decreased to 83 U/L. The patient's ALT and AST were normal at additional follow-up conducted on Day 357, with an ALT of 41 U/L (normal range 32-42 U/L) and an AST of 25 (normal range 31-37 U/L). Of

note, there was no associated eosinophilia, fever or rash in this patient at any time during the study.

Table 9i: Hepatobiliary Laboratory Transition Profile for Patient 08206017

Lab Test	Normal Range For this lab.	Baseline	EOT Day 8	TOC Day 27	Day 35	Day 357
ALT	**0 - 47 (U/L)**	**14**	**16**	**953**	**317**	**41**
AST	**0 - 37 (U/L)**	**23**	**25**	**716**	**83**	**25**
Total Bili	**0 – 19 (umol/L)**	**10**	**6**	**8**	**10**	**(?)**
GGT	**0 – 51 (U/L)**	**18**	**19**	**148**	**96**	**(?)**
Alk Phos	**40 – 135 (U/L)**	**81**	**100**	**131**	**99**	**(?)**
LDH	**110 – 250 (U/L)**	**183**	**176**	**439**	**202**	**(?)**
(?) = Value not provided in the Case Report Form.						

MO's Comments: *Patient 08066007 was enrolled with an abnormal ALT of 1402 U/L (*>20xULN). *At the time of enrollment, a history of chronic Tylenol abuse was given, according to the patient's CRF reviewed. His ALT decreased to normal level by the end of treatment.*

On the other hand, patient 08206017 had a normal ALT and AST at enrollment, up to at least Day 8 following his 1-dose dalbavancin. His known peak values of ALT and AST were on Day 27. These improved by Day 35. It is uncertain about what time the enzyme elevations resolved. However, the next time ALT/AST values were documented was on Day 357 (almost one year later). These increases in enzyme values were attributed to alcoholic hepatitis from heavy alcohol ingestion by the patient while on vacation, prior to his TOC visit.

The reviewer has reservations about a) the evaluation of this patient by the sponsor (and investigators) and b) the conclusion they reached. The reservations are based on the following:

1. *<u>History</u>*

   Although this apparently significant alcohol ingestion was reportedly confirmed by the investigator, on reviewing the patient's CRF, it is noteworthy that at enrollment, the patient denied a history of active substance abuse (drugs of any kind, including alcohol) which would have excluded him from the study, in accordance with exclusion criterion # 20. According to some literature[1], although the presentation of acute alcoholic hepatitis(AH) can vary from an asymptomatic patient to a critically ill individual, most patients with AH complain of anorexia, nausea and jaundice with or without fever and right upper quadrant abdominal pain. In other cases AH can manifest as a syndrome of progressive inflammatory liver injury associated with long-term heavy intake of ethanol. It usually persists and progresses to cirrhosis if heavy alcohol use continues. There was no information provided to suggest previous long-term alcohol use in the patient's history.

2. Absence of Report of Supportive Physical Findings at TOC Visit

Despite the occasional asymptomatic presentation of AH described above, presence of upper quadrant abdominal tenderness, hepatomegaly, and jaundice are strongly suggestive of AH. Approximately 40-50% of the patients have ascites in addition to tender hepatomegaly[2]. The picture of AH in this regard is similar to that of cholecystitis. In the evaluation of this patient, no evidence is provided for the presence of such signs and symptoms.

3. Laboratory Values

The initial liver enzyme parameters did not provide suggestive evidence of previous habitual alcohol use or abuse. Besides, liver enzyme levels in AH are reported in the literature to exhibit a characteristic pattern comprising moderate elevation of AST, while ALT is usually within reference range or mildly elevated. It is also reported that an AST/ALT ratio > 1 is almost universal in subjects with alcoholic hepatitis, which is opposite of what is observed in most other hepatitides and that an AST>500U/L should raise suspicion of an alternative diagnosis[1]. In this patient, not only was the ALT very high (953U/L) on Day 27, it was higher than AST, and the AST itself was > 500 U/L. The leukocytosis with a shift to the left that is usually common in AH patients, particularly severe ones, was absent in this patient.

4. Failure to rule out alternative diagnoses

Information about viral hepatitis (A,B,C) serology, or other possible viral etiologies (Cytomegalovirus, Epstein-Barr, etc) or acetaminophen abuse/ ingestion or other causes of this liver enzyme picture would have provided completion to this subject's evaluation to reassure the reviewer that dalbavancin could not have contributed to this subject's liver enzyme elevations. However, that the patient enzyme levels eventually normalized post dalbavancin treatment was reassuring.

For all the reasons given above, that dalbavancin caused or contributed to the liver enzyme elevations in this patient can not be ruled out.

Other Hepatobiliary abnormalities in Studies 8 and 9

Patients who had ALT/AST elevations in the >10xULN - 20xULN range

No dalbavancin-treated or comparator-treated patients had an ALT >10×ULN to 20×ULN in studies 8 and 9, although there were 2 such cases in the comparator arm in studies 4, 5 and 16 shown in table 9j later in this review. However, 2 (0.2%) patients who received one dose each of dalbavancin had elevated AST in the >10 x ULN - 20xULN range, similar to the 1(0.2%) who received 14 days of comparator treatment.

Patients who had ALT/AST elevations in the >5x-10xULN range

Five (0.5%) patients who were dalbavancin-treated had ALT elevations in the > 5x-10x ULN range. Three patients received 1 dose of dalbavancin; the other two received 2 doses. Five patients (1.1%) who all received 14 days of comparator treatment had ALT elevations in the >5x-10xULN range. For AST elevations, 3 patients (0.3%) in the

dalbavancin arm and 3 (0.6%) in the comparator arm had enzyme elevation in the >5x-10xULN range. Therefore the ALT and AST elevations in this category were similar across study arms.

Sponsor's narratives of two of the patients in this group who received dalbavancin associated with higher documented peak ALT levels were given as follows:

Patient 08-220-001, a 27-year-old Caucasian female who participated in Europe and received 1 dose of dalbavancin, had potentially clinically significant elevations in ALT and AST levels at the TOC visit (Day 13). On Day 13, the patient's ALT was 423 U/L (baseline value was 51 U/L), and her AST was 191 U/L (baseline value was 11 U/L). Also at this visit, the patient's platelets were elevated at 422 $\times 10^3/\mu L$ (baseline value was 204 $\times 10^3/\mu L$), her alkaline phosphatase was elevated at 482 U/L (baseline value was 127 U/L), and her GGT was elevated at 444 U/L (baseline value was 121 U/L). Total bilirubin remained normal throughout the study. No AEs were reported for this patient, who completed the study as a clinical success through the late follow-up phone call. Follow-up laboratory values after the study that were provided by the investigator indicated that the abnormalities were resolving. The investigator did not consider the elevated hepatobiliary values to be related to study drug; rather, the abnormalities were considered to be likely due to the patient's uterine cancer with possible liver metastasis.

Patient 09-005-085, a 34-year-old Hispanic/Latina female who participated in North America and received 1 dose of dalbavancin, had simultaneous elevations of ALT and AST at the TOC visit (Day 18). On Day 18, the patient's ALT was 481 U/L (baseline value was 63 U/L; EOT value on Day 6 was 129 U/L), and her AST was 255 U/L (baseline value was 30 U/L; EOT value on Day 6 was 58 U/L). The investigator reported AEs that included elevations of ALT, AST, and LDH, beginning on Day 18. Total bilirubin remained normal throughout the course of the study. No additional laboratory data were available for this patient, as attempts to contact her for follow-up were unsuccessful. The patient did not respond to a certified letter and disconnected her phone without providing forwarding information.

Patients who had ALT/AST elevations in the >3x-5xULN range

Nineteen (2.0 %) dalbavancin-treated patients had ALT elevations >3x-5xULN compared to 11 (2.3 %) comparator –treated patients. For patients who had AST elevations >3x - 5x ULN, 13 (1.4 %) were in the dalbavancin arm, similar to 7 (1.5 %) in the comparator arm. Sponsor's narratives of two of the patients in this group who received dalbavancin associated with higher documented peak ALT levels are as follows:

Patient 09-005-078, a 44-year-old Caucasian male who participated in North America and received 2 doses of dalbavancin, had elevated ALT and AST levels at the on-treatment visit (Day 8). At baseline, the patient's ALT and AST were elevated, with values of 57 U/L and 30 U/L, respectively. On Day 8, the patient's ALT level was 273 U/L, and his AST was 189 U/L. At the EOT and TOC visits, the patient's ALT and

AST values significantly decreased such that AST was normal (30U/L) and ALT was near normal (66 U/L, normal 30-65 U/L). Total bilirubin, which was elevated at baseline (1.9 mg/dl, normal 0-1mg/dl) actually normalized while ALT and AST were elevated, and were only slightly elevated (1.3 mg/dl) at TOC.

Patient 08-024-007, a 27-year-old black female who participated in North America and received 1 dose of dalbavancin, had potentially clinically significant elevations in ALT and AST at the TOC visit. At baseline, the patient's ALT was 62 U/L, and her AST was 38 U/L. At the TOC visit, her ALT was 268 U/L, and her AST was 120 U/L. The investigator did not repeat the laboratory tests after the TOC visit because he did not believe them to be of clinical significance. No AEs were reported for this patient during the study. At the sponsor's request, the patient was asked to return for a follow-up evaluation. The patient returned for follow-up on Day 244, and was asymptomatic; her ALT was 262 U/L and her AST was 106 U/L. Additionally, the patient's hepatitis panel revealed that the patient had chronic active hepatitis B. Other laboratory tests, including CBC, electrolytes, bilirubin, BUN/creatinine, and hepatitis A and C were within normal limits.

Bilirubin Changes

Changes in bilirubin values from baseline were similar across study arms.
Twenty eight (3%) of dalbavancin-treated patients compared to 12 (2.5%) comparator–treated patients had bilirubin elevations. As shown in table 9a, the rates were fairly similar when the subgroups receiving the similar durations of treatment are compared across the study arms.
The one patient with hyperbilirubinemia (Patient 09-037-030), treated with 2 doses of dalbavancin, had a potentially clinically significant value in total bilirubin of 1.60 mg/dL (normal range 0.2 - 1 mg/dL) at the TOC visit on Day 30; the patient's baseline value was 0.70 mg/dL. This patient's ALT was >1.5×ULN at baseline (62 U/L), but was normal at post-baseline visits; the AST was normal throughout the study. The patient's Alk Phos was normal (normal range= 32-92 IU/L): at baseline 59 IU/L, at 50 IU/L on Day 8, and 45 IU/L at the TOC visit. The investigator considered the patient's hyperbilirubinemia to be possibly related to study drug.

Only one hepatobiliary AE in either treatment group (acute cholecystitis) was reported as an SAE; both were considered unrelated to study medication.

Patients Who Met the Hy's Law

There were no cases that met Hy's law (defined as ALT increase > 3x ULN in combination with total bilirubin elevation > 1.5x ULN and normal or no significant elevation in alkaline phosphatase in the same patient) in studies 8 and 9.

Hepatobiliary Enzyme and Bilirubin Abnormalities in Studies 4, 5 & 16

In studies 4, 5 and 16 (table 9j), no dalbavancin-treated patients had an ALT elevation >10×ULN. Only 2 (1.1%) patients in the dalbavancin group, both in the 2-dose sub-group, had ALT elevation >5x-10xULN compared to 4 (3.8 %) in the comparator arm. There were no bilirubin increases from baseline values reported in studies 4, 5 and 16. The rest of the hepatobiliary abnormalities are as shown in table 9j.

Table 9j: Hepatobiliary Enzyme and Bilirubin Abnormalities for Studies 4, 5 and 16

	Dalbavancin (N = 938)						**Comparator (N = 469)**					
By ALT	**1 dose n =75**	**%**	**2 doses n =113**	**%**	**Total n=188**	**%**	**7 days n =23**	**%**	**14 days n =81**	**%**	**Total n=104**	**%**
>20xULN	0	-	0	-	**0**	-	0	-	0	-	**0**	-
>10xULN - 20xULN	0	-	0	-	0	-	0	-	2	2.4	2	1.9
>5x-10xULN	0	-	2	1.8	**2**	**1.1**	1	4.3	3	3.7	**4**	**3.8**
>3x-5xULN	1	1.3	4	3.5	**5**	**2.6**	1	4.3	7	8.6	**8**	**7.7**
>3x-5xULN -↑ from baseline	2	2.6	1	0.9	**3**	1.6	0	-	3	3.7	**3**	**2.9**
By AST	**1 dose n =75**	**%**	**2 doses n =113**	**%**	**Total n=188**	**%**	**7 days n =23**	**%**	**14 days n =81**	**%**	**Total n=104**	**%**
>20xULN	0	-	0	-	**0**	-	0	-	0	-	**0**	-
>10xULN - 20xULN	0	-	0	-	**0**	-	0	-	0	-	**0**	-
>5x-10xULN	0	-	0	-	**0**	-	0	-	4	4.9	**4**	**3.8**
>3x-5xULN	0	-	4	3.5	**4**	**2.1**	1	4.4	3	3.7	**4**	**3.8**
>3x-5xULN -↑ from baseline	0	-	3	2.7	**3**	**1.6**	1	4.4	1	1.2	**2**	**1.9**
By Bili >1.5 x ULN	**1 dose n =75**	**%**	**2 doses n =113**	**%**	**Total n=188**	**%**	**7 days n =23**	**%**	**14 days n =81**	**%**	**Total n=104**	**%**
↑ from Baseline Bilirubin values	0	-	0	-	0	-	0	-	0	-	0	-
By Alk Phos												
Clinically significant Alk Phos ↑	1	1.3	15	13.3	16	8.5	4	17.3	14	17.3	18	17.3
Hy's Law Cases	0	-	0	-	0	-	0	-	0	-	0	-
Alk Phos = Alkaline Phosphatase; Bili = Bilirubin; ULN = Upper Limit of Normal; ↑ = Increase(d).												

Hepatobiliary Disorder Adverse Events

The table 9k below is a summary of Hepatobiliary AEs in the Phases 2 and 3 studies. The frequencies of these AEs are similar across study arms.

Table 9k (Sponsor's Table 24): Hepatobiliary Disorder AEs (Phase 2/3 Integrated Database)

[Number (%) of Patients]

	Dalbavancin			**Comparator**		
	1 Dose (N = 419)	**2 Doses (N = 707)**	**Total (N = 1126)**	**7 Days (N = 176)**	**14 Days (N = 397)**	**Total (N = 573)**
Patients with at least 1 hepatobiliary disorder AE	**3 (0.7)**	**7 (1.0)**	**10 (0.9)**	0	**4 (1.0)**	**4 (0.7)**
Hepatic disorder NOS	0	2 (0.3)	**2 (0.2)**	0	1 (0.3)	**1 (0.2)**
Hepatitis NOS	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Cholecystitis acute NOS	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Cholelithiasis	1 (0.2)	0	**1 (0.1)**	0	1 (0.3)	**1 (0.2)**
Hepatic function abnormal NOS	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Hepatitis alcoholic	1 (0.2)	0	**1 (0.1)**	0	0	**0**
Hepatosplenomegaly NOS	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Hepatotoxicity NOS	1 (0.2)	0	**1 (0.1)**	0	1 (0.3)	**1 (0.2)**
Hyperbilirubinemia	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Hypoproteinemia	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Cholecystitis NOS	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Cholestasis	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Gallbladder disorder NOS	0	0	**0**	0	1 (0.3)	**1 (0.2)**

Hepatobiliary Disorders in Phase 1

Table 9L shows the distribution of subjects with enzyme elevations in the order of categories of elevations. Table 9m shows the hepatobiliary laboratory profile of subject 12001004 who had the highest liver enzyme elevations in all the studies conducted. His ALT (and AST) elevations were > 20 x ULN. The subject received two doses of dalbavancin. The details surrounding his liver enzyme elevations from normal baseline values are reported below.

One subject had ALT elevation >5x ULN - 10x ULN while 3 others had elevations >3x-5xULN.

Table 9L: Hepatobiliary Enzyme and Bilirubin Abnormalities in Phase 1 Subjects

ALT	**Dalbavancin < 1000 mg dose N = 66**		**Dalbavancin ≥ 1000 mg dose N = 78**	
normal at baseline	**n**	%	**n**	%
>20xULN	0	-	1	1.3
>10xULN - 20xULN	0	-	0	-
>5xULN - 10xULN	0	-	1	1.3
>3x-5xULN	1	1.5	2	2.6
abnormal at baseline				
>5xULN - 10xULN	0	-	1	1.3
>3x-5xULN	0	-	3	3.9
AST				
AST ↑ from normal baseline value				
>20xULN				
>10xULN - 20xULN				
>5x-10xULN			1	1.3
>3x-5xULN	0	-	1	1.3
AST ↑ from abnormal baseline value				
>20xULN			1	1.3
>10xULN - 20xULN				
>5x-10xULN				
>3x-5xULN			6	**7.7**
Bilirubin elevation				
>1.5xULN	2	3		

Phase 1 subject with ALT and AST with > 20 x ULN

Subject 12001004

The sponsor wrote the following narrative about this patient:

VER001-12 was a Phase 1 study of the safety, tolerability and pharmacokinetics of dalbavancin in individuals with impaired hepatic function. In this study individuals received a 1000 mg IV dose of dalbavancin on Day 1, and a 500 mg IV dose on Day 8. Subjects were housed in the site's Phase 1 clinical trials unit on Days -1 through completion of all assessments on Day 2 (i.e., 2 nights). Subjects did not stay overnight in the unit subsequent to the second dose. Subjects were to return periodically at scheduled visits for examination, solicitation of adverse events, and phlebotomy for pharmacokinetic data and laboratory safety testing, including serum chemistry.

An integral part of the study was the inclusion of a control group of individuals with normal hepatic function. Subject 12001004 was a 43 year old male who served as a healthy control. On screening, he reported no significant past medical history. His only recent prior medication was Alka-Seltzer Plus for symptoms of an upper respiratory infection. This individual was noted to have abnormal tests of hepatic function as part of his Day 60 laboratory data, including an ALT value of 2525 IU/L. Unfortunately this was not initially noted to be abnormal, as the site mistakenly thought these data were from a hepatically impaired subject and therefore not unusual.

When queried about this event by the sponsor, the investigative site immediately asked the subject to return to the site for additional testing. He returned on Days 109 and 126. Laboratory data obtained from Day 109 were positive for anti-HCV. A subsequent immunoblot for hepatitis C confirmed the result of the anti-HCV assay.
Results of anti-HAV IgM and HBsAg were also negative. The patient's hepatic function assays are shown below:

Table 9m Hepatobiliary Laboratory Transition Profile (Patient 12001004)

Lab Test	Normal values For this lab.	Baseline	Day 4	Day 22	Day 60	Day 109	Day 126
ALT	17 - 63 (IU/L)	43	28	58	2525	210	332
AST	15 - 41(IU/L)	33	18	37	1709	149	184
Total Bili	0.4 – 2(mg/dL)	0.5	0.4	1.6	2.1	0.8	1.2
Alk Phos	38 - 126(IU/L)	74	71	81	168	79	77
Anti-HCV						(+) RIBA	

Hemoglobin and total white blood cell count were normal at all time points tested.

At the time of his last visit to the investigative site, the patient was physically well and denied risk factors for HCV. He subsequently moved to California and was lost to follow-up. He was advised to seek further follow up of his hepatitis C infection.

Of note, this patient was housed in the same room as subject 12001001 on Day 1 to Day 2. Subject 12001001 was a subject with hepatic impairment in Group A (mild hepatic impairment). The etiology of his hepatic impairment was chronic hepatitis C.

Although there is no accepted serologic definition of acute hepatitis C, this subject's rapid ALT rise and fall are compatible with acute hepatitis C[1]. ALT values exceeding 1000 U/L are not unusual in acute hepatitis C[2], and such a diagnosis is plausible in this subject. Additionally, there are documented cases in the medical literature of nosocomial transmission of hepatitis C between roomates[3], as well as in ambulatory health care settings[4].
Although no serum is available for this subject, antibodies to hepatitis C were confirmed by HCV immunoblot assay performed at the (b) (4). No serum is available for further testing.

Sponsor's References

1. Gordon SC. New insights into hepatitis C. Gastro 2003; 125: 253-56

2. Gerlach JT, Diepolder HM, Zachoval R et al. Acute hepatitis C: High rate of both spontaneous and treatment induced viral clearance. Gastro 2003; 125: 8-88.

3. Forns X, Martinez-Bauer E, Feliu A et al. Nosocomial Transmission of HCV in the Liver Unit of a Tertiary Care Center. Hepatology 2005; 41: 115-122.

4. Williams IT, Perz JF, Bell BP. Viral Hepatitis Transmission in Ambulatory Health Care Settings. Clin Inf Dis 2004; 38:1592-1598.

MO's Comments: *This 43 year-old Caucasian male subject had apparently been in good health (based on the history reported) and with normal liver enzymes (from his liver function test results up to day 22 of dalbavancin treatment. He was however assigned to the subgroup of patients with mild hepatic impairment in study 12(Phase 1), according to the CRF. The rise in his liver enzymes on day 60 was rather swift. It is unknown what the true peaks of his liver enzyme elevations were, as his ALT of 2525 U/L and AST of 1709 U/L only represent the levels at the point in time his blood was drawn on day 60. That he was found to be positive for hepatitis C virus (HCV) infection, confirmed by recombinant immunoblot assay (RIBA), is helpful information. It is unclear what criteria*

were applied in study 12 that led to his assignment to the subgroup of subjects with mild hepatic impairment.
Most literature articles reviewed by the medical reviewer thus far regarding the likelihood of such a dramatic rise in ALT and AST in acute hepatitis C, including the references cited by the sponsor, are either silent or lack specific statements about the issue. However, the closest to being specific reviewed so far was the article by J.T. Gerlach et al, where 24 self-limited acute HCV patients had ALT that reached a mean peak of 964 ± 469 (U/L) after seroconversion at about 8 weeks; whereas the 36 chronic cases who sero-converted at a mean time of 21 weeks, did reach a mean peak ALT of 837 ± 593 (U/L) [3].

Regarding nosocomial transmission, there are literature reports, including the one cited by the sponsor, that document patient-to-patient transmission of HCV. It is usually in the setting of extended hospitalization (≥10 days) [4]. *This subject was housed in the same room with another subject with chronic HCV infection for 2 nights. Regardless of how the subject acquired the disease, it is noteworthy that there is a temporal sequence between dalbavancin administration (a drug with an unusually long half-life) and the development of his liver enzyme abnormalities. Although the enzyme values began to decrease by Day 109, questions remain. For example, are his very high ALT and AST values (obtained on day 60) solely due to HCV or did dalbavancin make any contribution? Does dalbavancin exacerbate liver enzyme derangement in the presence of HCV infection or other viral hepatitides? Or is the occurrence of liver enzyme elevations in certain individuals who have received dalbavancin an idiosyncratic phenomenon? In this scenario, HCV infection would be only a red herring, just clouding the picture. These ALT and AST levels in this subject are probably uncommon in acute hepatitis C infection. Although the positive HCV serology and RIBA offer a probable explanation for the liver enzyme derangement, one cannot exclude dalbavancin as a cause or a contributor to these liver laboratory abnormalities in this subject.*

Table 9n: A summary of unresolved Liver laboratory abnormalities associated with receipt of Dalbavancin.

PTID/ # of doses/ ULN range	Abnormal Laboratory Values							Query
	Day from First Dose							
	Test	**Normal Range**	**Baseline**	**Day 8**	**Day 27**	**Day 35**	**Day 357**	
08206017	ALT	0 - 47 (U/L)	14	16	953	317	41	Neither the patient's history, nor the sponsor's report of the patient condition or the enzyme abnormalities supports the sponsor's diagnosis of Alcoholic Hepatitis.
1 dose >20 x ULN	AST	0 - 37 (U/L)	23	25	716	83	25	
	GGT	0 – 51(U/L)	18	19	148	96	(?)	
								This patient was a 27 y/o with uterine cancer. No AE reported. No follow up (f/u) lab values provided in the CRF although, per the sponsor, the post study f/u labs "provided by the investigator indicated that the abnormalities were resolving." These f/u labs were not found in the CRF.
08-220-001			**Baseline**	**Day 13**				
1 dose 5x-10x ULN	ALT	0 - 47 (U/L)	51	423				
	AST	0 - 37 (U/L)	11	191				
	Bilirubin	0 – 19 (umol/L)	19	12				
	Eos	Percent	0.2	3.2				
09-005-085			**Baseline**	Day 6	**Day 18**			No follow up lab values obtained. Patient was lost to follow up. AEs recorded as "Elevations of ALT, AST and LDH".
1 dose	ALT	30 - 65 (U/L)	63	129	481			
5x-10x ULN	AST	0 - 37 (U/L)	30	58	255			
	Bilirubin							
12001004								
2 doses			**Baseline**	**Day 22**	**Day 60**	**Day 109**	**Day 126**	This case is confounded by (+) hepatitis C by recombinant Immunoblot assay (RIBA). Whether acute Hep C led to the dramatic rise in the ALT and AST remains an unresolved question and the answer may never be known
> 20x ULN	ALT	17- 63 (IU/L)	**43**	**58**	**2525**	**210**	**332**	
	AST	15-41 (U/L)	33	37	1709	149	184	
	Bilirubin	0.4 -2 (mg/dL)	0.5	1.6	2.1	0.8	1.2	
	Hep C					(+) RIBA		
09005026			**Baseline**	**Day 16**	**Day 28**	**Day 109**	**Day 126**	No further f/u lab values; no hepatitis serology results
2 doses	ALT	30- 65 (IU/L)	139	228	218			
3-5 x ULN	AST	0 - 37 (U/L)						
	Bilirubin							
09005078			**Baseline**	**Day 8**	**EOT**	TOC		Investigator reports enzyme elevation possibly related No f/u lab values.
2 doses	ALT	30- 65 (IU/L)	57	273		66		
3-5 x ULN	AST	0 - 37 (U/L)	30	189		30		
	Bilirubin	0-1 (mg/dL)	1.9	-		1.3		
			Baseline	**EOT**		**Day 24**	Day 244	
08024007	ALT	10- 60 (IU/L)	62	133		268	262	Hepatitis panel on Day 244 revealed chronic active Hepatitis B, per the sponsor's report.
I dose	AST		38			120	106	
3-5 x ULN	Bilirubin							

Overview of Renal Disorder Adverse Events

In Table 10a below, the sponsor shows the frequency of renal disorders considered AEs and derived from the Phase 2/3 integrated database. Among the patients who received dalbavancin, 2.6% had at least 1 renal AE, slightly lower in rate than the 3.1% of patients who received a comparator drug. With regard to the dose or duration of therapy received, 9 (2.1%) who received 1 dose of dalbavancin had at least one AE, compared to 5 (2.8%) who received 7 days of the comparator treatment. Twenty (2.8%) patients who received 2 doses of dalbavancin had at least 1 AE compared to 13 (3.3%) who received 14 days of the comparator treatment.

Table 10 a (Sponsor's Table 25): Renal Disorder Adverse Events: Phase 2/3 Integrated Database [Number (%) of Patients]

	Dalbavancin			Comparator		
	1 Dose (N = 419)	2 Doses (N = 707)	Total (N = 1126)	7 Days (N = 176)	14 Days (N = 397)	Total (N = 573)
Patients with at least 1 renal disorder AE	**9 (2.1)**	**20 (2.8)**	**29 (2.6)**	**5 (2.8)**	**13 (3.3)**	**18 (3.1)**
Dysuria	1 (0.2)	5 (0.7)	**6 (0.5)**	0	1 (0.3)	**1 (0.2)**
Hematuria	2 (0.5)	3 (0.4)	**5 (0.4)**	2 (1.1)	4 (1.0)	**6 (1.0)**
Pollakiuria	1 (0.2)	2 (0.3)	**3 (0.3)**	0	0	**0**
Renal failure NOS	2 (0.5)	1 (0.1)	**3 (0.3)**	2 (1.1)	0	**2 (0.3)**
Urinary retention	1 (0.2)	2 (0.3)	**3 (0.3)**	0	1 (0.3)	**1 (0.2)**
Proteinuria	0	2 (0.3)	**2 (0.2)**	0	1 (0.3)	**1 (0.2)**
Acute prerenal failure	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Candiduria	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Ketonuria	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Nephrolithiasis	1 (0.2)	0	**1 (0.1)**	0	0	**0**
Oliguria	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Pyuria	0	1 (0.1)	**1 (0.1)**	0	2 (0.5)	**2 (0.3)**
Renal failure acute	1 (0.2)	0	**1 (0.1)**	1 (0.6)	3 (0.8)	**4 (0.7)**
Renal impairment NOS	0	1 (0.1)	**1 (0.1)**	1 (0.6)	0	**1 (0.2)**
Renal pain	1 (0.2)	0	**1 (0.1)**	0	0	**0**
Urethral stricture	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Urine abnormal NOS	1 (0.2)	0	**1 (0.1)**	0	0	**0**
Bladder discomfort	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Hydronephrosis	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Micturition urgency	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Renal cyst NOS	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Renal disorder NOS	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Urinary incontinence	0	0	**0**	0	1 (0.3)	**(0.2)**

Acute Renal Failure

Altogether, eleven cases had different kinds of renal disorders that led to renal failure (including, by preferred terms, acute pre-renal failure, renal failure NOS, and renal disorders leading to failure acute). One (0.1%) dalbavancin-treated patients (08-045-001), developed acute renal failure (ARF) compared to 4 (0.7%) comparator-treated patients.

The ARF of Patient 08-045-001 was attributed to contrast-dye induced nephropathy. It was considered unrelated to dalbavancin.
One comparator (vancomycin)-treated case (# 04-009-503) was considered by the investigator to be probably drug-related. The other patients were considered by the investigator to be unrelated or unlikely related to study drug.
The narrative of the dalbavancin-treated case who experienced contrast-induced nephropathy (mentioned above) was given by the sponsor as follows:

Patient 08-045-001 was an 82-year-old Caucasian male, treated with 1 dose of dalbavancin. On Day 8, the patient was withdrawn from treatment due to worsening clinical status. No Gram-positive or Gram-negative pathogens were isolated from his baseline SSSI culture. While hospitalized, the patient underwent abdominal and lower extremity angiograms, a CT scan, and cardiac catheterization. He was found to have occluded grafts from previous coronary artery bypass surgery. The patient developed symptoms of contrast-induced nephropathy with oliguria, was transferred to the ICU in respiratory distress, and was intubated. He was diagnosed with severe acute renal failure and cardiopulmonary failure. He responded to medical management and was extubated. However, a few days later, he developed atrial fibrillation and a gastrointestinal bleed. Renal failure worsened due to the patient's cardiopulmonary insufficiency. He died of cardio-pulmonary failure on Day 23. The investigator considered all of these events, including the AE associated with death, to be unrelated to study drug

MO's Comment: *This patient was severely ill. He had procedures, including abdominal and lower extremity angiograms, and cardiac catheterization. He also had occluded grafts from previous coronary artery bypass surgery as well as gastrointestinal bleeding. In addition, he was on, or had received, multiple concomitant medications, including, propoxyphene, nifedipine, albuterol, ipratropium, enoxaparin, flagyl, morphine, ranitidine, metporolol, ,Nitroglycerin, KCL, clopidogrel, midazolam, lorazepam, lasix, dopamine, pantoprazole, etc. His clinical deterioration and subsequent death are difficult to attribute directly to one out of many drugs received which included dalbavancin.*

Serum Creatinine Values
As shown in Table 10b- 10d, among the patients whose creatinine values increased from baseline in studies 8 and 9, 6 (0.6%) were dalbavancin-treated compared to 2 (0.4%) who received comparator treatment. The rates in both arms were similar. Patients who had creatinine elevation at baseline did not seem to show a trend of deterioration from baseline following receipt of dalbavancin or the comparator (table 10d).

Table 10b: High Serum Creatinine in studies 8+9

	Dalbavancin N = 938						Comparator N = 469					
	1 dose n =344	**%**	**2 doses n =594**	**%**	**Total n=938**	**%**	**7 days n =153**	**%**	**14 days n =316**	**%**	**Total n=469**	**%**
Creatinine												
Elevated Creatinine from normal baseline value (Table 10c below)	1	0.3	5	0.8	**6**	**0.6**	0	-	2	0.6	**2**	0.4
Elevated Creatinine at baseline (Table 10d below)	3	0.9	5	0.8	**8**	**0.9**	1	0.6	5	1.6	**6**	1.3
BUN												
BUN elevation from baseline	2	0.6	0	-	**2**	**0.2**	1	0.6	2	0.6	**3**	0.6
BUN= Blood Urea Nitrogen												

Table 10c High Serum Creatinine Transition Profile in studies 8+9

PTID	Dalbavancin Arm	Normal Range	Baseline	Day 8	EOT	TOC
08002001	2doses	(0.5 -1.5)	1.5	1.9	1.8	**1.9**
08012008	2doses	(0.5 -1.5)	1.5	1.5	**2.2**	2.0
08033024	2doses	(0.5 -1.5)	1.6	**2.1**	1.3	1.3
09037021	2doses	(0.5 -1.5)	0.8	-	**2.0**	-
09020004	2doses	(0.5 -1.5)	1.3	1.3	**2.8**	1.4
09014001	1 dose	(0.5 -1.5	1.6	**3.2**	1.4	1.5
Comparator						
08069001	14 days	(0.5 -1.5)	1.2	**1.7**	1.3	1.5
09005023	14 days	(0.5 -1.5)	1.0	2.1	**3.5**	1.1
PTID= Patient I.D. number; EOT= end of treatment visit; TOC= Test of cure visit						

Table 10d: Patients With High Baseline Creatinine values in Studies 8 & 9

PTID	Dalbavancin	Normal Range	Baseline	Day 8	EOT	TOC
08252001	2 doses	(44-89)*	150	96	327	114
09010015	2 doses	(0.5 – 1.5)	3.0	2.5	2.1	2.0
09037006	2 doses	(0.5 – 1.5)	2.5	1.7	-	-
09060003	2 doses	(0.5 – 1.5)	2.0	1.5	-	1.5
09203017	2 doses	(44-89)*	127	147	124	110
08046002	1 dose	(0.5 – 1.5)	2.1	-	2.7	2.6
08252002	1 dose	(44 - 89)	257	-	202	-
09012001	1 dose	(0.5 – 1.5)	2.3	-	-	1.6
PTID	**Comparator**	**Normal Range**	**Baseline**	**Day 8**	**EOT**	**TOC**
08069002	7 days	(0.5 – 1.5)	2.0	-	2.1	2.3
08050011	14 days	(0.5 – 1.5)	2.7	1.8	1.9	1.8
09052002	14 days	(0.5 – 1.5)	2.4	2.4	2.3	2.8
09250005	14 days	(44-89)*	165	93	82	67
09250010	14 days	(44-89)*	145	144	152	157
09047003	14 days	(44-89)*	137	142	141	159
* mmol/L, all other lab ranges given in the column are in mg/ dL PTID= Patient I.D. number; EOT= end of treatment visit; TOC= Test of cure visit						

H**igh Serum BUN in studies 8 and 9**

Two (0.2%) of dalbavancin-treated patients had blood urea nitrogen (BUN) elevation and both patients received 2 doses (table 10e). Three (0.6%) comparator-treated patients had BUN elevations; 2 received 14 days of comparator treatment while the third was treated for 7 days. Although the rates were slightly higher in the comparator arm, the numbers were small.

Table 10e: High Serum BUN in studies 8 and 9

PTID	Dalbavancin	Normal Range	Baseline	Day 8	EOT	TOC
08252002	1 dose	8 – 25	17.9	-	28.3	-
09014001	1 dose	8 – 25	34	**73**	23	36
PTID	**Comparator**	**Normal Range**	**Baseline**	**Day 8**	**EOT**	**TOC**
08069002	7 days	8 – 25	49	-	71	76
09038038	14 days	8 – 25	34	34	**62**	29
09005023	14 days	8 – 25	17	47	**77**	15

H**igh Serum BUN and Creatinine in studies 4, 5, 16**

In studies 4, 5 and 16, increases in creatinine from baseline occurred only in few patients and are comparable across study arms (Table 10f).

Table10f: BUN and Creatinine in studies 4, 5, 16

	Dalbavancin (N = 938)						**Comparator (N = 469)**					
	1 dose n =75	**%**	**2 doses n =113**	**%**	**Total n=188**	**%**	**7 days n =23**	**%**	**14 days n =81**	**%**	**Total n=104**	**%**
Creatinine ↑ from baseline	0	-	2	1.7	**2**	1.1	2	8.7	1	1.2	**3**	2.9
BUN↑ from baseline	0	-	1	0.9	**1**	0.5	0	-	0	-	**0**	-

Table10f.2: High Serum BUN in studies 4, 5 and 16

PTID	**Dalbavancin Arm**	**Normal Range**	**Baseline**	**Day 8**	**EOT**	**TOC**	**Comments**
16047002	2doses	8 – 25	45	43 (D4)	51	64	
04008214	2doses***	8 – 25	15	48	78	31	Early discontinuation
04038505	2doses	8 – 25	41	33	53	83	
PTID	**Dalbavancin Arm**	**Normal Range**	**Baseline**	**Day 8**	**EOT**	**TOC**	**Comments**
04008525	7 days	8 – 25	84	44*	60	none	* Obtained on Day 4
*** The only increased BUN from baseline							

MO Comments: *The renal vacuolization noted in the animal toxicology data was in the reviewer's mind while evaluating renal laboratory parameters for safety signals in studies 8and 9 as well as studies 4, 5 and 16. No significant safety trends in the key renal parameters (BUN/ creatinine) have emerged and no outlier attributable to dalbavancin has been seen.*

Phase 1 Integrated Safety Database

The frequency of renal disorder AEs was similar between subjects treated with dalbavancin and subjects given placebo (5.0% dalbavancin; 5.3% placebo). Of note, there was one subject (11-001-003) who reported end stage renal disease; this subject had a medical history significant for ongoing chronic renal failure.

Pancreas: Glucose Metabolism

In light of the toxicology reviewer's report of pancreatic vacuolization and degeneration in rats and dogs, patients' chemistry laboratoratory results were explored for evidence of abnormal glucose metabolism (i.e., hyperglycemia or hypoglycemia).
Tables 10g and 10g.2 show patients that had increases in glucose levels from baseline while receiving dalbavancin or the comparator treatment. As shown in the tables, 6/938 (0.6%) of dalbavancin-treated subjects had significant increase in blood glucose from

baseline compared to 1/469 (0.2%) patient who was comparator-treated.

Table 10 g: Patients with Increases in Serum Glucose* for studies 8 and 9

Dalbavancin						Comparator					
1 dose n=344	**%**	**2 doses n= 594**	**%**	**Total n=938**	**%**	**7days n=153**	**%**	**14 days n=316**	**%**	**Total n=469**	**%**
1	0.3	5	0.8	6	0.6	0	-	1	0.3	1	0.2
Individual subject serum glucose transition profile given below											

Table 10 g,2
Glucose Transition profiles in patients who developed hyperglycemia on treatment

PTID	**Dalbavancin Arm**	**Baseline**	**Day 8**	**EOT**	**TOC**	**(+) DM**	**Comments**
08071003	1dose	161	-	487	498	**Yes**	
08009011	2 doses	125	462	165	176	**Yes**	
09009023	2 doses	135	455	99	126	No	No SP comments
09023006	2 doses	108	-	375	395	**Yes**	
09050007	2 doses	132	425	111	124	No	AE= Hyper
09037021	2 doses	358	-	1146	-	Yes	
PTID	**Comparator Arm**	**Baseline**	**Day 8**	**EOT**	**TOC**	**(+) DM**	
09005065	Comparator 14 days	98	347	98	-	No	
DM = Diabetes Mellitus; Hyper = Hyperglycemia; SP= Sponsor; AE= Adverse Event - = value not provided							

In tables 10h and 10i, 5 (0.6%) dalbavancin-treated patients had clinically significant decreases in serum glucose compared to none in the comparator arm of the study.

Table 10h: Subjects with Decreases in Serum Glucose* in studies 8 & 9

Dalbavancin						Comparator					
1 dose n=344	**%**	**2 doses n= 594**	**%**	**Total n=938**	**%**	**7days n=153**	**%**	**14 days n=316**	**%**	**Total n=469**	**%**
1	0.3	4	0.7	5	0.5	0	-	0	-	0	-
*Individual subject serum glucose transition profile given in Table 10i, below.											

Table 10i: Serum Glucose Transition Profiles in Patients Who Developed Hypoglycemia

PTID	**Dalbavancin Arm**	**Baseline**	**Day 8**	**EOT**	**TOC**	**(+) DM**	**Comments**
08029003	1dose	70	-	30	86	No	-
09001007	2 doses	87	132	36	114	No	AE= a-HG
09017006	2 doses	98	38	92	62	No	
09081002	2 doses	100	50	31	70	No	AE = a-HG
09250002	2 doses	115	324	39.5	6.5	**Yes**	
PTID	**Comparator Arm**	**Baseline**	**Day 8**	**EOT**	**TOC**	**(+) Diabetes**	
-	None	-	-	-	-	-	
AE= Adverse event; DM = Diabetes Mellitus; a-HG = asymptomatic Hypoglycemia							

Serum Glucose Responses in studies 4, 5 and 16

Two patients (1.1%) had increases in serum glucose in the dalbavancin arm in these studies (one received 1 dose, the other, 2 doses). One patient (1%) who received 14 days of comparator treatment had an increase in serum glucose.

Only one patient who received 14 days of the comparator drug had a decrease in serum glucose. None in the dalbavancin arm had any glucose decrease.

MO Comments: *In studies 8 and 9, the incidence of hyperglycemia in 6 (0.6%) patients who received dalbavancin compared to 1(0.2%) comparator-treated patient is noteworthy. The numbers may be small but important. Of note also, 4/6(~67%) of these dalbavancin-treated hyperglycemic patients were diabetic. A detailed review of the patient's CRF revealed no helpful information that would enable adequate assessment of the temporal relationship of the receipt of dalbavancin to the development of abnormal blood glucose levels. On asking the sponsor for an explanation regarding hyperglycemia in the non-diabetic patients, one of them (patient 09050007) was reported to have ingested 32 oz of Gatorade and cookies just prior to blood sample being drawn; the second patient (09009023) reportedly had blood drawn from the patient's I.V. line (presumably mixed with D5W fluid).The diabetic patients were reported to have poor control of their diabetes mellitus.*

Similarly, hypoglycemia occurred in 5 dalbavancin-treated patients, one of whom was diabetic. For the non-diabetic patients, the sponsor's explanations included incorrect sample processing, poor oral intake/malnutrition for one of the patients with prostate cancer, and another with a family history of low blood sugar. There was no explanation for one case that also happened to have had mild hyperglycemia the week before, on Day 8 study visit.

Like hyperglycemia cases, the total numbers are also small. However, it is noteworthy. It is also important to note that, even though vacuolization, degeneration and apoptosis of the acinar cells of the pancreatic tissue have been reported in rats and dogs given dalbavancin daily for 3 months, no Islet cells involvement have been reported. In addition, and equally importantly, the Pharmacology/Toxicology reviewer has stated that these findings are non-specific. There are no chemistry laboratory values for serum amylase or lipase provided by the sponsor.

Serum Glucose Responses in Phase 1 Subjects

According to the sponsor, several Phase 1 subjects in both treatment groups had increases in glucose. The highest proportion of subjects with a shift from normal to high glucose levels occurred at Day 14, as 10.2% of subjects who received dalbavancin and 10.0% of subjects who received placebo had this shift. However, many of these subjects had diabetes mellitus.

Hematology

Seven hematology parameters were included in analysis: hemoglobin, hematocrit, WBC, neutrophils, lymphocytes, eosinophils, and platelets.

Anemia

Some of the patients in the studies had normal hemoglobin values at baseline but subsequently dropped while receiving dalbavancin or the comparator treatment. Some had low hemoglobin at baseline that remained unchanged or worsened while on treatment.

As shown in table 11a, 25/938 (2.7%) of dalbavancin-treated patients who had normal hemoglobin at baseline developed anemia on treatment compared to 9/469 (1.9%) of the comparator-treated patients. When patients who had anemia at baseline that worsened on treatment were added to the aforementioned group, 38/938 (4.1%) dalbavancin-treated patients developed anemia on treatment compared to 17/469 (3.9%) of comparator-treated patients. Thus, the development of anemia on treatment is similar across study arms. For the patients whose anemia worsened on dalbavancin treatment, a higher rate of patients had worse anemia in the subgroup that received 2 doses than in patients that received 1 dose (2% versus 0.3%). In the patients who entered the study with normal baseline hemoglobin, there was no difference between the 2-dose vs the 1-dose subgroups (2.7% vs 2.6%). The rates of development of anemia in the subgroups were similar across study arms.

MO's Comments: *Most patients experienced no significant change in their hemoglobin status during the study. Some patients who had normal baseline hemoglobin developed clinically significant anemia during treatment. Other patients had anemia at baseline that worsened during treatment. Thus, 38/938(4.0 %) patients developed clinically significant anemia while receiving dalbavancin compared to 17/469 (3.6 %) in the comparator group. The anemia only appeared to be dose related for patients who had anemia at baseline. Across study arms, the incidence of anemia in the 1-dose dalbavancin-treated patients was similar to that of the patients who received 7 days of the comparator treatment. Similarly, the incidence of anemia in the patients that received 2 doses of dalbavancin was comparable to that of the patients who received 14 days of the comparator. Interestingly, among the comparator-treated patients who had clinically significant decrease in hemoglobin from normal baseline values, only two patients were linezolid-treated. Many of the anemia cases resolved by EOT and TOC visits, with no record of intervention.*

Leukopenia/ Neutropenia

The patients who developed clinically significant low white blood cell (WBC) values during treatment in studies 8 and 9 are shown in table 11a. Among the dalbavancin-

treated patients, only 2 (0.2%) had leukopenia versus 3 (0.6%) comparator-treated patients. Most of the leukopenia patients were in study 4, discussed later in this review, under studies 4, 5 and 16.
Neutropenia occurred with slightly higher frequency among the comparator- treated patients (0.9%) than in patients who received dalbavancin treatment (0.25%).

MO's Comments:
Leukopenia was rare in studies 8 and 9 subjects. There were a few cases of leukopenia in patients receiving chemotherapy. Only 2 (0.2%) patients, each of whom received 2 doses of dalbavancin treatment, developed non-chemotherapy related leukopenia compared to 3(0.6%) comparator-treated patients. The leukopenia in each case was felt to be dalbavancin-related by the sponsor, even though one of the patients had a concomitant viral rhinorrhea. The rate of leukopenia was slightly higher in the comparator-treated patients than in dalbavancin-treated patients but the numbers are small. The degree of leukopenia was generally mild to moderate. In one of the two dalbavancin-treated patients, the leukopenia had resolved prior to the TOC visit. The other patient had lower value of WBC at the TOC visit than the value recorded in earlier visits and had no follow-up values to determine the length of time to resolution of the leukopenia. The incidence of leukopenia in the dalbavancin arm was similar to that observed in the comparator arm.

Thrombocytopenia

Overall, 9/938 (1%) of dalbavancin-treated patients developed significant thrombocytopenia (platelet count < 100, 000) and is comparable to 6/469 (1.3%) of comparator- treated patients. In the 1-dose arm, 2/344 (0.6%) developed clinically significant thrombocytopenia compared to 1 /153 (0.7%) who received comparator treatment for 7 days; and 7/594 (1.2%) patients who received 2 doses of dalbavancin treatment compared to 5/316 (1.6%) who received comparator treatment.

MO's Comments: *In the dalbavancin treatment arm, 9/938 (1%) patients developed thrombocytopenia compared to 6/469 (1.3%) in the comparator arm. In patients receiving 1 dalbavancin dose, 2/344 (0.6 %) developed thrombocytopenia compared to 1/153 (0.7 %) who received 7 days of comparator treatment. For patents who received 2 doses of dalbavancin treatment, 7/594 (1.2%) had thrombocytopenia compared to 5/316 (1.3%) patients who were comparator- treated for 14 days. The rates were similar across study arms. Within the subgroups, there was a higher rate of thrombocytopenia in patients with normal platelet counts at baseline in the 2-dose dalbavancin subgroup compared to the 1-dose subgroup. Although there was also a higher incidence of thrombocytopenia in patients receiving 14 days of the comparator treatment versus those receiving 7 days of the comparator, the figures are small to be clinically meaningful. For the comparator-treated, 18/19 patients were linezolid-treated, including one case with a platelet count of 20x $10^3/mm^3$ who received intervention. All 18 received 14 days of linezolid. In patients with laboratory follow-up, thrombocytopenia generally resolved. There were no pancytopenia cases recorded in studies 8 and 9.*

Table 11a: Hematologic changes in subjects in studies 8 and 9

	Dalbavancin N = 938						**Comparator N = 469**					
Anemia (Hemoglobin ≤ 0.8 x LLN)	**1 dose n =344**	**%**	**2 doses n =594**	**%**	**Total n=938**	**%**	**7 days n =153**	**%**	**14days n =316**	**%**	**Total n=469**	**%**
Developed anemia on treatment	9	2.6	16	2.7	**25**	2.7	3	2	6	1.9	**9**	**1.9**
BL anemia worse on treatment	1	0.3	12	2.0	**13**	**1.4**	1	0.7	7	2.2	**8**	**1.7**
Hemoglobin ↓ on treatment	10	2.9	28	4.7	**38**	**4.1**	4	2.7	13	4.1	**17**	**3.6**
All anemias	19	5.5	56	9.4	**75**	**8.0**	4	2.6	41	13	**45**	**9.9**
Leukopenia (=WBC<4.5 x 10^3)												
Overall leukopenia	0	-	2	0.2	**1**	**0.1**	1	0.7	2	0.6	**3**	0.6
Thrombocytopenia												
Drop in Platelet count to < 100,000 on Rx	1	0.3	7	1.2	**9**	**1.0**	1	0.7	5	1.6	**6**	**1.3**
All Significant ↓, + from high to low normal	1	0.3	11	1.9	**12**	**1.3**	1	0.7	18	5.7	**19**	**4.1**
Pancytopenia	0	-	0	-	**0**	-	0	-	0	-	**0**	-

Hb = Hemoglobin; WBC= White Blood Cell Count; Rx = treatment; ↓= decrease(d); BL= Baseline, + = including decrease

Hematologic changes in subjects in studies 4, 5 and 16

Table 11b below shows the patients whose hematologic parameters were abnormal in studies 4, 5 and 16 with regards to hemoglobin, leukocytes and platelets.

Anemia
For most patients with anemia at baseline, their anemia remained unchanged on treatment. This is reflected in first row in table 11b where 39/188 (20.7 %) patients who received dalbavancin treatment had anemia compared to 33/104 (31.7%) who were comparator-treated. In the subgroups, 9/75 (12%) who received 1 dose of dalbavancin treatment and 6/23 (26%) in the 7-day comparator –treated subgroup had anemia. Also, 34/113 (30%) patients who received 2 doses of dalbavancin treatment compared to 27/81(33%) patients who received comparator treatment for 14 days had anemia. The rate of anemia was higher in the comparator group compared to dalbavancin-treated patients but is likely related to the small number of patients. For patients who had decrease in their hemoglobin levels on treatment, the numbers are much smaller in number as shown on the same table with the overall rates being 4/188 (2.1%) in patients who received dalbavancin compared to 2/104 (1.9%) in comparator-treated patients.

Leukopenia/ Neutropenia

There was a higher 8/188 (4.3%) rate of leukopenia in patients who were dalbavancin – treated compared to comparator- treated patients (2.9%) and these cases only occurred in patients who received 2 doses of dalbavancin-treatment or 14 days of comparator treatment [table 11b]. Neither patients who received 1 dose of dalbavancin nor 7 days of comparator treatment developed leukopenia. In addition, 5 (2.7%) dalbavancin-treated patients had neutropenia compared to 2 (1.9%) comparator- treated patients.

Thrombocytopenia

Nine of 188 (5%) dalbavancin-treated patients developed thrombocytopenia compared to 6/ 104 (5.8%) patients who received comparator treatment.

There were no cases of dalbavancin-related pancytopenia in studies 4,5 and 16.

MO's Comments: *Table 11b displays the spread of patients across study arms whose hemoglobin, leukocytes or/ and platelets decreased in studies 4, 5 and 16. The frequency rates in these events (anemia, leukopenia and thrombocytopenia) were large because the denominator numbers are small. However, a large proportion of the study patients had anemia, most before the study and a smaller number during the study. The latter subset of patients is fairly balanced across study arms.*
There is a higher distribution of leukopenia in the dalbavancin treated patients compared to the comparator- treated patients. Most cases of leukopenia were from Study 4. Some of the patients in this study were on chemotherapy but too few to explain the

disproportionate number. Of note, these patients received either 2 doses of dalbavancin or 14 days of the comparator treatment.
The same can almost be said of patients that developed thrombocytopenia except that one of the patients received 7 days of comparator treatment. But the rates of thrombocytopenia are similar across study arms.
Two subjects who received 2 doses of dalbavancin had pancytopenia. One of them who had sarcoma had received chemotherapy 4 days prior to enrollment in study 4 while the other was receiving chemotherapy concomitantly with dalbavancin also in study 4.
In most of the patients not receiving chemotherapy, their *thrombocytopenia resolved*.

.

Table 11b: Hematologic Changes in subjects in studies 4, 5 and 16

	Dalbavancin N = 188						**Comparator N = 104**					
Anemia	**1 dose n =75**	**%**	**2 doses n =113**	**%**	**Total n=188**	**%**	**7 days n =23**	**%**	**14 days n =81**	**%**	**Total n=104**	**%**
PCS Anemia	9	12	34	30	**39**	**20.7**	6	26	27	33	**33**	**31.7**
Patients with normal or low Hb at BL that significantly decreased on Rx	1	1.3	3	2.7	**4**	**2.1**	0	-	2	2.5	**2**	**1.9**
Leukopenia												
Subjects with normal or low WBC at BL that significantly decreased in the course of Rx	0	-	8	7.0	**8**	**4.3**	0	-	3	3.7	**3**	**2.9**
Neutropenia	1	1.3	4	3.5	**5**	**2.7**	0	-	2	2.5	**2**	**1.9**
Thrombocytopenia												
Normal platelet count at BL, ↓ on Rx ; plus low platelet at BL, remained low or ↓ on Rx	0	-	9	8	**9**	**5**	1	4.3	4	5	**6**	**5.8**
Two patients, 04005509 and 04005527, were on chemotherapy for sarcoma and leukemia respectively and had pancytopenia attributable, per the sponsor to their chemotherapy. Hb = Hemoglobin; WBC= White Blood Cell Count; Rx = treatment												

Changes in Hematologic parameters in Phase 1 studies
MO's Comments: *A majority of Phase 1 subjects had normal hematologic parameters. Two subjects (1.4%) had a decrease in their hemoglobin values after each received 500-1000 mg of dalbavancin; only in one (0.7%) of the 2 subjects (11001019) was the change in hemoglobin value considered potentially clinically significant. Similarly, only in 1 (0.7%) subject (12001011) was a drop in platelet count (132, 000/ mm^3 to 66,000/ $mm^{3)}$ considered clinically significant. Of the 7/141 (~5%) subjects who had mildly low WBC values, none was reported to have developed a decrease in their WBC value after receiving dalbavancin.*

7.1.7.3.1 Analyses focused on measures of central tendency

There were only very few differences between the study drug and the comparator drug to affect measures of central tendency for laboratory values significantly. No changes in the mean laboratory values that involved a significant number or proportion of patients. Most abnormal laboratory values resolved by the time patients had their TOC visits. Some shift from normal range was so small that they were not clinically significant

7.1.7. 3.2 Analyses focused on outliers or shifts from normal to abnormal

Refer to the discussion of hepatobiliary cases of 2 phase 3 patients (Patient ID # s 08066007 and 08206017 on pages 81 -83 and pages 91- 93) and Phase 1 subject (# 12001004, pages 87-89) all of who had liver enzyme (ALT and AST) >20 x ULN. These can be found under section 7.1.7

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities
See the previous section, i.e. 7.1.7. 3.2

7.1.7.4 Additional analyses and explorations

Refer to the section on glucose metabolism on pages 97-99
No further suspicious safety laboratory signals were noted to necessitate or warrant additional analyses and exploration.

7.1.7.5 Special assessments

We were concerned about the hepatotoxicity experienced by the 3 patients whose liver enzyme elevations were >20x ULN. There was a plausible explanation for Patient 08066007. He had a history of Tylenol abuse and his enzymes were elevated at baseline. The case of the Phase 1 subject #12001004, was confounded by a positive hepatitis C RIBA test. The third case was assigned a diagnosis of alcoholic hepatitis. The lack of supportive evidence for that diagnosis, e.g. by the patient's presentation and the pattern of

ALT and AST elevations were not consistent with that diagnosis.

As part of special assessment and in response to our concern , we solicited the input of the Associate Director for Science, Office of Pharmacoepidemiology and Statistical Sciences, John R. Senior, MD. He wrote an official consult as follows:

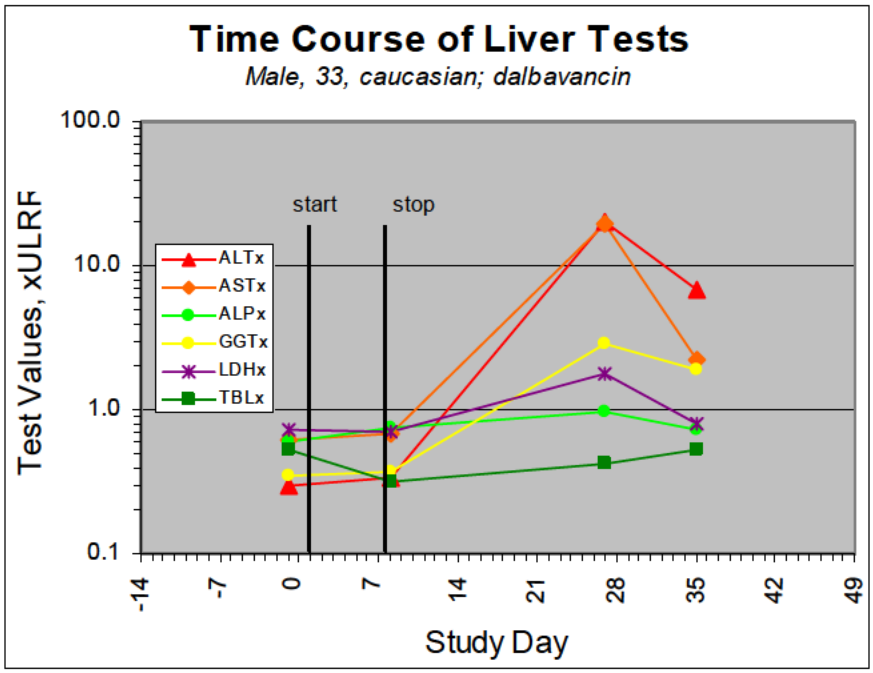
SUBJECT: Case of acute hepatotoxicity in a patient; after treatment with new drug, dalbavancin (N 21-883); please assess causality attribution

This request for consultative opinion calls attention to a case of markedly increased activities of serum alanine and aspartate aminotransferase (ALT and AST) found in a 33-year-old Caucasian man 26 days after a single dose of 1000 mg of dalbavancin, a new glycopeptide antibiotic with long-acting activity against Gram-positive bacteria. Limited information was available, but the ALT and AST had been within normal limits the day before the drug administration and one week afterward. There was no observed rise in the serum total bilirubin concentration (TBL), but there were slight increases in serum activities of gamma-glutamyltransferase (GGT) and lactate dehydrogenase (LDH) with the transaminase rises, and slight increase of activity of the serum alkaline phosphatase (ALP) within the normal range. Repeat testing 8 days later showed declining serum activities of all five enzymes, and repeat about 11 months later showed normal ALT and AST activities. The study participant had been treated in Europe for a staphylococcal cutaneous infection, and was reported to have been drinking heavily while on vacation before the "test of cure" (TOC) visit on Study Day 27 (Day 1 = day on which treatment was given). The site investigator reported the abnormalities observed as a mild adverse event with subsequent resolution, unrelated to study drug (dalbavancin). Because of the history of heavy drinking, the investigator attributed the abnormalities to alcoholic hepatitis, but no concerted effort was made to rule out other possible causes (such as acute viral hepatitis A or B, acetaminophen biliary or circulatory problems, etc.) Dr. Imoisili, from his review of literature and inspection of the time course of test results, doubted that the invesitigator's diagnosis was correct, and asked me to review the case. (The data may be seen in his e-mail message to me of 29 April, reproduced as Appendix A.)

Comment: *The syndrome of acute alcoholic hepatitis (AAH) was first recognized and well described in England over 40 years ago (Beckett AG, et al., 1961). The symptoms include anorexia, nausea and vomiting, fever, right upper quadrant abdominal pain, and jaundice, with findings of often quite high leukocytosis, large and tender liver, occurring after a bout of excessive drinking (Mezey, 2003). Depending on how many previous episodes of AAH may have occurred, findings attributable to chronic liver disease or cirrhosis may be seen. The serum ALT characteristically is not much elevated in AAH and is usually less than the AST, which is only modestly elevated. If ALT is greater than AST, and if either are more than 300 U/L, other causes should be sought, especially acute viral hepatitis A or B (seldom C, which is more often insidious and chronic rather than acute). Other causes such as ingestion of acetaminophen should also be looked for, and biliary tract disease, autoimmune hepatitis, acute onset of Wilson's disease, and ischemic hepatitis following hypotension or congestive failure should be ruled out. Only about 15-*

20% of heavy alcohol consumers are susceptible to attacks of acute alcoholic hepatitis, and subsequent development of chronic alcoholic liver disease and alcoholic cirrhosis. Histologic findings of macrovesicular fat infiltration, centrilobular hepatic necrosis with neutrophilic infiltrates, Mallory alcoholic hyaline, and central venous sclerosis are characteristic, if liver biopsy is done. Because the serum transaminases do not become much elevated, Maddrey (1978), and later Carrithers et al. (1989), developed severity indices for AAH that relied on serum total bilirubin and upon plasma prothrombin time, rather than serum transaminase activities. Since 1980 (Ludwig, et al.), it has been known that some people, especially obese people, may occasionally show findings of non-alcoholic steatohepatitis (NASH) that closely mimic the histologic picture of AAH but occur without exposure to high amounts of alcohol.

The findings in this study participant, #08-206-017, do not fit the picture of AAH, but are most likely the result of some other process, Insufficient information was collected to rule out many of the other possible causes that could account for the findings, but it remains <u>possible</u> that they were caused by the investigational drug dalbavancin. More probable and correct diagnosis would require additional clinical study and information that were not obtained in this case.



It may be noted in the graphic display of the tests done, in which all of the test values are expressed in multiples of the upper limit of the reference range (xULRR) and plotted on a logarithmic-base 10 scale the emphasize the normal range and modest elevations without too much suppression by the high transaminase values, that there was an abrupt onset of hepatic cell injury (ALT, AST elevations) without obstructive or cholestatic features (ALP elevation) that may have occurred somewhere between 8-25 days after the dalbavancin administration. The TBL did not ever rise at all, and so overall liver function was not much affected by the transient injury to hepatocytes. It is not clear from the data

available that the peak values of the enzyme rises that really occurred were captured, but may have been missed in the interval from Study Day 9-26, as was the time of onset of the acute hepatocellular injury. It is also unclear when the abnormalities may have returned to the normal range prior to the last observation 356 days after the drug was administered. It is unfortunate that the site investigator leapt to the conclusion that this set of liver test abnormalities was due to acute alcoholic liver injury, without investigating or making further observations, as a result of which he/she was probably wrong. The cause of the transaminase rise remains unknown, and is very likely not alcoholic excess in this man. It remains possible that dalbavancin caused, or contributed to the findings, but only possible, lacking sufficient clinical information to be more certain. In reaching this opinion, I concur with the medical reviewer, Dr. Imoisili, and disagree with the investigator.

Recommendation:

1) In evaluation of the NDA, do not exclude this case from consideration as possibly induced by the investigational drug, despite the poor information gathering, and look for more cases that may be better documented.

With respect to the Phase 1 subject (# 12001004) whose case was confounded by a new diagnosis of Acute Hepatitis C (by positive RIBA), we did not obtain a consult because of the confounding HCV diagnosis.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The vital signs measured comprised pulse, respiration rate, systolic and diastolic blood pressure, and oral body temperature. Table 12a outlines the criteria by which the parameters were evaluated, i.e. expected range of normal values, potentially clinically significant lower and upper values, as well as changes considered potentially clinically significant in lower and upper limit values. These values were then compared between the dalbavancin- treated patients and comparator-treated patients.

Table 12a Sponsor's table of Criteria for Identifying PCS and PCSC Vital Sign Results

Parameter (units)	Normal Range	PCS Low Value	PCS High Value	PCSC Decrease in Value	PCSC Increase in Value
Pulse (bpm)	60 - 100	<50	>120	0.5x	2x
Respiration rate (bpm)	---	<8	>32	---	---
Systolic blood pressure (mmHg)	95 -145	<85	>200	0.2x	1.6x
Diastolic blood pressure (mmHg)	60 - 95	<50	>120	0.2x	1.2x
Oral temperature (°Celsius)	---	---	---	2^0	2^0

bmp = beats per minute

Note: The change from baseline was tabulated as a PCSC only if the post-baseline value for the parameter was outside of the defined normal ranges.

MO's Comments: *The values defined by the sponsor as potentially clinically significant (PCS) lower and upper values are fairly extreme by comparison to normal ranges, e.g. a systolic blood pressure (mmHg) > 200, a diastolic blood pressure (mmHg) > 120, etc. However, the reviewer's attempt to use lower limits did not make any significant difference in the comparisons. The reviewer then adopted the sponsor's defined limits for assessment of vital signs parameters*

The sponsor's definitions of parameters measured in vital signs evaluation are as follows:

Baseline parameter: the last data collected prior to the first dose of study drug.

On-treatment observation: parameter measurements done or collected on Day 8 (or closest to Day 8 while on treatment). For Study 16, the data for the on-treatment observation were collected on Day 4.

End-of-treatment (EOT) data: the *first* data collected after the last dose of study drug.

Test-of-cure (TOC) data: the *last* data collected after the last dose of study drug.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Studies selected and grouped to enable analyses of vital signs and overall drug-control comparisons follow the foregoing pattern adopted from the beginning of the review. Thus, comparisons were made among patients who received dalbavancin versus the comparator antibiotic in studies 8 and 9. Similar comparisons were made in studies 4, 5 and 16 patients, as well as subjects in Phase 1 studies.

7.1.8.3 Standard analyses and explorations of vital signs data and Analyses focused on outliers or shifts from normal to abnormal Studies 8 and 9 Subjects

Blood Pressure

As shown in table 12b, among the 938 dalbavancin-treated patients in studies 8 and 9, 7 (0.7%) had potentially clinically significant (PCS) systolic BP > 200 mmHg, similar to 4/469 (0.9%) of the comparator-treated group. Among the subset of patients who received 2 doses of dalbavancin, 6/594 (1%) had PCS systolic BP > 200 mmHg compared to 2/316 (0.6%) who received 14 days of the comparator drug treatment. The numbers are small and the relationship with study drug could not be determined. The numbers are similarly small in patients who experienced decreases in systolic BP < 85, being 2/938 (0.2%) and 2/469 (0.4%) in patients who received dalbavancin and the comparator treatments respectively.

No patients in studies 8 and 9 who received one dose of dalbavancin experienced a PCS increase in diastolic BP > 120 mmHg, whereas 3/ 594 (0.5%) patients who received 2 doses of dalbavancin had PCS increase in diastolic BP > 120 mmHg. No patient who received 7 days of the comparator treatment experienced an increase in diastolic BP > 120 mmHg, but 1/316 (0.3%) who received 14 days of the comparator treatment experienced an increase in diastolic BP > 120 mmHg.
Among the patients who had PCS decrease in diastolic BP <50, 35/938 (3.7%) were dalbavancin-treated compared to 22/469 (4.7%) subjects who received the comparator treatment. In the subgroups, 7/344 (1.4%) received 1 dose of dalbavancin compared to 3/153 (2.0 %) who were comparator-treated; similarly, 28/594 (4.7%) received dalbavancin compared to 19/316 (6%) who were comparator-treated. Among the patients who had the lowest diastolic blood pressure (29 -31) in studies 8 and 9, not shown on the table but reported in the dataset, 2/938 (0.2%) were dalbavancin-treated compared to 4/ 469 (0.8%) who were comparator-treated. These events in these particular patients were not reported as adverse events or as drug related events.

Pulse
Fifteen (1.6%) of dalbavancin-treated patients had PCS increase in pulse > 120 compared to 9/469 (1.9%) in the comparator-treated group. No AEs of tachycardia were reported. PCS decreases in pulse < 50 were similar in occurrence in both dalbavancin-treated (0.7%) and comparator-treated (0.6%) patients.

Respiratory Rate
Neither patients who received 1 dose of dalbavancin or 7 days of the comparator drug had PCS respiration rate > 32. Three (0.5%) patients who received 2 doses of dalbavancin and one patient (0.3%) who received comparator treatment had PCS respiration rate > 32.

Temperature
Among the dalbavancin-treated patients, 14 (1.5%) had oral temperature (°Celsius) > 37.7 ^{0}C compared to 15 (3.2%) of comparator-treated patients. In studies 8 and 9, patients' temperatures were < 40^{0}C. But among the patients whose temperatures were >

39^0C, 4 (0.4%) were dalbavancin-treated compared to 5 (1.1%) who received comparator treatment.

Table 12b Changes in Vital Signs testing in Patients in studies 8 and 9

	Dalbavancin N = 938						Comparator N = 469					
Blood Pressure (BP) Systolic BP	**1 dose n =344**	**%**	**2 doses n =594**	**%**	**Total n=938**	**%**	**7 days n =153**	**%**	**14 days n =316**	**%**	**Total n=469**	**%**
PCS ↑ in Systolic BP ≥ 200	1	0.3	6	1.0	**7**	**0.7**	2	1.3	2	0.6	**4**	**0.9**
↓ in Systolic BP < 85	1	0.3	1	0.2	**2**	**0.2**	0	-	2	0.6	**2**	**0.4**
Diastolic BP												
PCS ↑ in Diastolic BP ≥ 120	0	-	3	0.5	**3**	**0.3**	0	-	1	0.3	**1**	**0.2**
PCS ↓ in Diastolic BP ≤ 50	7	1.4	28	4.7	**35**	**3.7**	3	2.0	19	6.0	**22**	**4.7**
Pulse Rate												
PCS ↑in pulse > 120	3	0.9	12	2.0	**15**	**1.6**	3	2.0	6	1.9	**9**	**1.9**
PCS ↓ in pulse < 50	1	0.3	6	1.0	**7**	**0.7**	2	1.3	1	0.3	**3**	0.6
Respiratory Rate												
PCS ↑ in Respiratory Rate > 32	0	-	3	0.5	**3**	**0.3**	0	-	1	0.3	**1**	**0.2**
PCS ↓ in Respiratory Rate < 8	0	-	0	-	0	-	0	-	0	-	0	-
Temperature												
Oral Temperature ≥ 37.7 ^{0}C	3	0.9	11	1.9	**14**	**1.5**	6	3.9	9	2.8	**15**	**3.2**
Oral Temperature ≤ 36.9 ^{0}C	1	0.3	8	1.3	**9**	**1.0**	3	2.0	4	1.3	**7**	**1.5**

PCS = Potentially clinically significant; ↓ = Decrease; ↑ = Increase

Studies 4, 5 and 16 Studies

Blood Pressure

Referring to table 12c, 2/188 (1.1%) dalbavancin-treated patients in studies 4, 5 and 16 subjects had PCS systolic BP > 200 mmHg. There were no comparator-treated patients in these studies who had systolic BP > 200 mmHg. There were no reported cases of PCS increase in diastolic BP > 120 mmHg in both the dalbavancin-treated and comparator-treated patients.

Among the patients who had PCS decrease in diastolic BP <50, 22/188 (11.7%) were dalbavancin-treated compared to 21/104 (20.2%) patients who received the comparator treatment. These patients generally had diastolic blood pressures ≥ 40. One patient who received 2 doses of dalbavancin (04008569 with a diastolic BP 38 mmHg) and one comparator-treated patient (04008525 who had a diastolic BP 37 mmHg) had PCS decrease in diastolic BP <40. The dalbavancin-treated patient (04008569) who had an AE of hypotension was not considered to be drug related.

Pulse
Twenty three (12.2%) of dalbavancin-treated patients had PCS increase in pulse > 120 compared to 12/104 (11.5%) in the comparator-treated group. No AEs of tachycardia were reported or considered to be drug-related. PCS decreases in pulse < 50 were absent in the dalbavancin-treated group but occurred in only one patient (~1%) in the comparator-treated patients.

Respiratory Rate
Seven (3.7%) patients who received dalbavancin and 4 (3.8%) who received comparator treatment had PSC respiration rate > 32. None was considered drug-related.

Temperature
Nine patients (4.8%) who were dalbavancin-treated had oral temperature (°Celsius) > 37.7 ^{0}C compared to 4 patients (3.8%) who were comparator-treated.
PCS low oral temperature ≤ 36.9 ^{0}C were recorded in 16 (8.5%) of dalbavancin-treated patients compared to 4/104 (7.7%) who received comparator treatment. No event of event of hypothermia was recorded as an AE or considered to be drug related.

Table 12c Changes in Vital Signs testing in patients in studies 4, 5 and 16

	Dalbavancin N = 188						**Comparator N = 104**					
Blood Pressure (BP) Systolic BP	**1 dose n =75**	**%**	**2 doses n =113**	**%**	**Total n=188**	**%**	**7 days n =23**	**%**	**14 days n =81**	**%**	**Total n=104**	**%**
PCS ↑ in Systolic BP >200	1	1.3	1	1.9	**2**	**1.1**	0	-	0	-	**0**	-
↓ in Systolic BP< 85	3	4.0	10	8.8	**13**	**6.9**	1	4.3	5	6.2	**6**	**5.8**
Diastolic BP												
PCS ↑ in Diastolic BP > 120	0	-	0	-	**0**	**-**	0	-	0	-	**0**	-
PCS ↓ in Diastolic BP < 50	6	8	16	14	**22**	**11.7**	2	8.7	19	23.5	**21**	**20.2**
Pulse Rate												
PCS ↑ in pulse ≥ 120	5	6.7	18	15.9	**23**	**12.2**	1	4.3	11	13.6	**12**	**11.5**
PCS ↓ in pulse < 50	0	-	0	-	**0**	**-**	0	-	1	1.2	**1**	**1**
Respiratory Rate												
PCS ↑ in Respiratory Rate > 32	2	2.7	5	4.4	**7**	**3.7**	1	4.3	3	3.7	**4**	**3.8**
PCS ↓ in Respiratory Rate < 8	0	-	0	-	**0**	**-**	0	-	0	-	0	-
Temperature												
PCS High Oral Temperature ≥ 37.7 ^{0}C	1	1.3	8	7.0	**9**	**4.8**	0	-	4	4.9	**4**	**3.8**
PCS Low Oral Temperature ≤ 36.9 ^{0}C	5	6.7	11	9.7	**16**	**8.5**	1	4.3	7	8.6	**8**	**7.7**

PCS = Potentially clinically significant; ↑ = Increase; ↓ = Decrease

Vital signs in Phase 1 Subjects

According to the sponsor, there were few PCS values or changes from baseline in vital sign parameters and the changes from baseline in vital signs were generally mild, transient, and unremarkable.

Blood Pressure

A few subjects had fluctuations in blood pressure after dalbavancin administration. According to the sponsor, while these subjects had transient PCS blood pressure values, none was determined by the investigator to be clinically significant or required action or treatment.

Respiratory Rate and Oral temperature

No PCS values or changes from baseline in respiration rate and oral body temperature for the subjects in the Phase 1 were recorded.

Pyrexia, defined by the sponsor as an oral temperature ≥37.1°C (based on WHO toxicity criteria) used for the Phase 1 studies, was reported as an AE by 21 (14.9%) subjects who received dalbavancin and 5 (26.3%) subjects who received placebo. All but 1 subject with pyrexia was in study 2. No case of pyrexia had a temperature greater than 37.5°C (99.5°F).

Pulse

No Phase 1 subject had a high PCS value or increase from baseline in pulse. On Day 1 at the end of study drug infusion, 3 subjects who received >1000 mg dalbavancin (Subjects 02-100-143, 12-001-010, and 12-001-026) had a low PCS pulse whereas no subjects who received placebo had any low pulse. None of these PCS values met the criteria for PCS changes from baseline.

At 4 hours after study drug infusion on Day 1, 5 subjects who received dalbavancin had a low PCS pulse (Subjects 01-001-003, 01-001-005, 12-001-026, 13-001-008, and 13-001-024), compared with 1 subject who received placebo (Subject 01-001-004). At 4 hours after study drug infusion, the lowest pulse rate among these subjects was 43 bpm, reported for Subject 01-001-005 (baseline value 61bpm). None of the low pulse rates were reported as an AE.

7.1.8.3.1 Analyses focused on measures of central tendencies

There were only very few differences between the study drug and the comparator drug to affect measures of central tendency for vital signs significantly. No changes in the mean vital signs that involved a significant number or proportion of patients

*7.1.8.3.*3 Marked outliers and dropouts for vital sign abnormalities

Among the dropouts in all the studies conducted by the sponsor, none resulted from vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

No vital sign abnormalities were of such severity to merit additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

The ECGs conducted on the patients in this program were done around the time the patients received their first infusion of study medication, one before (baseline), and the second followed the completion of infusion (at C_{max}). According to the Sponsor, the timing of ECGs was selected to correspond to the C_{max} of dalbavancin but this did not correspond to the C_{max} for comparator drugs. Data from the Phase 3 studies were compared to a group of drugs with no known QT effects. The evaluation of the results was done by a centralized expert reviewer in a blinded fashion. Only patients with paired ECG data were evaluated. The data were analyzed by the sponsor to identify subjects with potentially clinically important results. There were no subjects who discontinued treatment or were withdrawn from a study because of changes in the QT interval.

The effect of study drug on QT interval was evaluated using Bazett and Fridericia corrections. The sponsor reports that the listings from integrated ECG database are provided for the following patients:

1). Patients with PCS post-baseline QTc interval values (explained below)
2) Patients with a post-baseline QTc interval value >500 msec, and
3) Patients with post-baseline T-wave abnormalities and/or U-wave abnormalities.

In addition, Phase 2/3 integrated ECG database were also examined by age group, gender, race/ethnicity, and location of study. Moreover, the sponsor summarized the following data:

- change from baseline in QTcB interval;

- the number (%) of patients with increased QTcB interval <30 msec, >30 to 60 msec, and >60 msec);
- the number (%) of male patients with post-baseline QTcB interval of <431 msec, 431 to 450 msec, >450 msec, or >500 msec; and
- the number (%) of female patients with post-baseline QTcB interval of <451 msec, 451 to 470 msec, >470 msec, or >500 msec.

Increases from baseline in QTc interval and the actual post-baseline QTc interval values were also summarized for Phase 2/3 patients in the following additional subgroups:
• BMI (<18.5 kg/m^2, 18.5 to <25 kg/m^2, and ≥25 kg/m^2).
• Baseline serum magnesium values (<LLN, ≥LLN).
• Baseline serum potassium values (below, within, and above the normal limits).
• Baseline serum calcium values (below, within, and above the normal limits).
• Baseline renal function (serum creatinine values ≤ULN, >ULN).
• Baseline hepatobiliary function (alkaline phosphatase >1.5×ULN, or GGT >1.5×ULN, or ALT >3×ULN, or AST >3×ULN).
• Concomitant cardiac medication usage (yes/no).
• Concomitant cardiac medication usage and/or a history of congestive heart failure and/or a history of myocardial infarction (yes/no).

Cardiac medications in the subgroups listed above included drugs classified using the WHO Drug Dictionary anatomical therapeutic class (ATC) as cardiac glycosides, anti-arrhythmics, and/or calcium channel blockers.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

According to the sponsor, the ECG data collected were from Phase 1 (studies 2, 10, 11, 12, and 13), Phase 2 (studies 4 and 5) and one Phase 3 study (study 8). No explanation was provided regarding failure to collected data from study 9 patients.

7.1.9.3 Standard analyses and explorations of ECG data
T and U wave abnormalities in Study 8

Per the sponsor's report, in the Phase 2/3 integrated safety database, 354 dalbavancin-treated patients and 178 comparator-treated patients had normal T and U waves at baseline and had post-baseline ECG conducted.
In study 8, 1 (0.3%) dalbavancin-treated patients (08-007-006) had a T-wave abnormality, described as an abnormal T pattern in standard leads, with normal sinus rhythm and a prior myocardial infarction. In comparison, 1 (0.5%) comparator-treated patient (08-206-010) had abnormal widespread T pattern, with a normal sinus rhythm. There was neither a U-wave abnormality nor a combined T- and U-wave abnormality.

T and U wave abnormalities in Studies 4 and 5

Among the patients evaluated in the phase 2/3 database, 354 dalbavancin-treated patients and 178 comparator-treated patients had normal T and U waves at baseline. Only one patient (04008525) who received 7 days of comparator treatment had a T-wave abnormality with abnormal widespread ST pattern, with normal sinus rhythm. There was neither a U-wave abnormality nor a combined T- and U-wave abnormality.

T and U wave abnormalities in Phase 1 Studies

Among the Phase 1 subjects evaluated for U and T wave abnormalities, 105 subjects who received dalbavancin and 13 subjects in the Phase 1 integrated safety database who received placebo had normal T and U waves at baseline and had a post-baseline ECG conducted. One (1.0%) subject (12-001-020) who received dalbavancin had a T-wave abnormality, described as abnormal T pattern in precordial leads, with normal sinus rhythm. None of the subjects who received placebo had a T-wave abnormality. No subject had a U-wave abnormality or both T- and U-wave abnormalities.

An expert report of ECG results for the Phase 1 integrated safety database concluded that no rhythm disturbance, including ventricular arrhythmia, was observed in any of the ECG recordings analyzed.
A slight modification of repolarization, including T-wave morphology, was elicited following serial analysis of each subject's ECGs. No change in U-wave amplitude or appearance of new U waves was observed during treatment.

QT Intervals

The sponsor reports that in the Phase 2/3 integrated database, 382 dalbavancin-treated patients had paired ECG data (Table 13a). The mean change in QTcB interval was reported as 0.4 msec (95% CI = -1.7 to 2.4 msec), and ranged from -88 to 95 msec. In the comparator arm, 199 comparator-treated patients had paired ECG data. The mean change in QTcB interval was -2.2 msec (95% CI = -5.3 to 0.8 msec), and ranged from -98 msec to 62 msec.
The sponsor reports that during drug exposure, 6.3% of dalbavancin-treated patients had an increase in QTcB >30 to 60 msec, compared to 5.5% of comparator-treated patients. Two (0.9%) male dalbavancin-treated patients and 1 (0.6%) female dalbavancin-treated patient had a treatment-emergent QTcB interval >500 msec. In comparison, 2 (1.8%) male comparator-treated patients and 1 (1.1%) female comparator-treated patient had a treatment-emergent QTcB interval >500 msec. The sponsor further reported that there was no meaningful difference between dalbavancin-treated patients and comparator-treated patients for frequency of QTcB outliers observed during drug exposure.

Table 13a Change in QTcB

	Dalbavancin-treated	Mean Δ msec	Range msec	CI msec	Comparator-treated	Mean Δ msec	Range msec	CI msec
Had paired ECG	**N = 382**	**0.4**	**-88-95**	**-1.7 to 2.4**	**N = 199**	**-2.2**	**-98 to 62**	**-5.3 to 0.8**
QTcB >30 to 60 msec	**6.3%**				**5.5%**			
QTcB >500 msec	**2 (0.9%)**				**2 (0.6%)**			
Δ = Change; CI = Confidence Interval.								

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Reviewer's analysis of the Dataset ECG Information

Study 8 Patients

Overall, 538 subjects had baseline ECG studies performed. Of these patients, 528 ITT patients had a second ECG during Day 1 treatment. As shown in table 13b, 326 (91.6 %) dalbavancin - treated and 162 (89.5 %) comparator-treated patients had QTcB interval ≤ 30 msec. Twenty (5.6%) dalbavancin - treated patients and 10 (5.5 %) comparator-treated subjects had QTcB intervals >30- 60 msec.

Table 13b: Post baseline QTcB changes in study 8 Patients

	Dalbavancin N = 356 (Screened)						**Comparator N = 181 (Screened)**					
QTcB	**1 dose n =266**	**%**	**2 doses n =90**	**%**	**Total n=356**	**%**	**7 days n =133**	**%**	**14 days n =48**	**%**	**Total n=181**	**%**
> 60 msec	2	0.8	0	-	**2**	0.6	0	-	1	2.1	**1**	0.6
30 - 60 msec	16	6	4	4.4	**20**	5.6	10	7.5	0	-	**10**	5.5
≤30 msec	242	91	84	93.3	**326**	91.6	118	88.7	44	91.7	**162**	89.5
Some subjects who had baseline EEG screening did not have a comparative ECG during Day 1 Treatment												

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Of the 3 patients who had post-baseline QTcB change > 60 msec, 2 (0.8 %) were dalbavancin-treated while 1 (0.6 %) was comparator-treated (table 13c).
One of the dalbavancin-treated subjects was a female who had a poor R-wave progression in precordial leads interpreted as abnormal and clinically significant but not significantly changed from baseline or pre-treatment ECG.

Table 13c Subjects with QTcB or QTcF >500 msec in Study 8

Subject PTID	Gender	Treatment received	Visit Day	QTcB	QTcF	Comments
08037006	Female	Dalbavancin 1 dose	Baseline Day 1	410 505	421 478	QTcB change (see outliers below)
08033019	Male	Dalbavancin 2 doses	Baseline Day 1	531 528	516 510	> 500msec at Baseline; no significant Δ on Rx
08080001	Male	Dalbavancin 2 doses	Baseline Day 1	502 477	453 431	QTcB > 500msec at Baseline Not made worse by Rx.
08083018	Male	Dalbavancin 2 doses	Baseline Day 1	506 494	464 458	QTcB > 500msec at Baseline Not made worse by Rx.
08082001	Male	Dalbavancin 2 doses	Baseline Day 1	506 450	467 422	QTcB > 500msec at Baseline
08069002	Male	Comparator 7 days	Baseline Day 1	496 505	471 478	QTcB > 500msec on Day 1 (on Rx)
08055003	Male	Comparator 14 days	Baseline Day 1	517 522	518 513	> 500msec at Baseline Not made worse by Rx

Outliers with significant QTcB change > 60 msec from Baseline

Subject PTID	Gender	Treatment received	Visit Day	QTcB	QTcF	QTcB Change
08024007	Female	Dalbavancin 1 dose	Baseline Day 1	373 438	371 418	65
08033027	Male	Comparator 14 days	Baseline Day 1	373 435	368 415	62
08037006	Female	Dalbavancin 1 dose	Baseline Day 1	410 505	421 478	95

Table 13d: **№ of Patients with abnormal QTcB (or QTcF) recordings in Study 8 at baseline**

QTcB (msec)	Dalbavancin (N = 382)						Comparator (N = 199)					
	1 dose n =266	%	2 doses n =90	%	Total n=356	%	7 days n =133	%	14 days n =48	%	Total n=181	%
> 500	1	0.4	4	4.4	**5**	1.4	1	0.8	1	2.1	**2**	1.1
♂: > 450 but <500	16	6.0	8	8.9	**24**	6.7	2	1.5	2	4.2	**4**	2.2
♀: > 470 but <500	2	0.8	2	2.2	**4**	1.1	3	2.3	2	4.2	**5**	2.8
♂ & ♀ rows	18	6.8	10	11	**28**	7.9	5	3.8	4	8.3	**9**	5.0

MO's Comments: *The ECG changes considered most significant with respect to study drug potential to cause QT prolongation include QTcB > 500 msec and/ or QTcB changes from baseline > 60 msec after the patient has received (or been receiving) the study drug. In study 8, in some patients, QTcB > 500 msec at baseline (before receiving study drug) were recorded. As shown in table 13c and table 13d all 4 patients who received 2 doses of dalbavancin and the one patient who received 14 days of comparator treatment were in this category. None of these patients' QTcB was apparently further prolonged by dalbavancin treatment. About 6.7% of dalbavancin-treated male patients had QTcB > 450msec compared to 2.2% of comparator-treated patients. Despite this difference in the rates, no AE was reported in these patients.*
*There were 3 outliers with QTcB change > 60 msec from baseline as shown in the lower end of table 13c.Patient 08024007 was a 27- year old African-American female who received 1 dose of dalbavancin; she had an abnormal QTcB change of 65 msec associated with a decreased T wave amplitude on Day 1 of therapy. It was reported as not clinically significant. Patient 08037006, an 89- year old Caucasian female also received 1 dose of dalbavancin; she had an abnormal and clinically significant QTcB change of 95 msec. She had atrial fibrillation, a poor R wave progression in precordial lead but with normal repolarization pattern. She had no bundle branch block. The ECG report described these events as an association of no qualitative drug effect. The 3rd patient (*08033027) *was comparator-treated.*

Patients with high QTcB or QTcF values in Studies 4, 5, 16

Table 13e shows patients categorized by QTcB values in studies 4 and 5. Two (1.8 %) patients who received dalbavancin had QTcB > 500 msec compared to 1(1.2 %) comparator-treated patient. For patients who had QTcB reading > 450 msec (male) or > 470 msec (female), 3 (5.4 %) 2-dose dalbavancin-treated patients versus 3 (6.7 %) patients who received 14 days of comparator treatment were in this category.

Table 13e: Patients with high QTcB or QTcF values in Studies 4, 5

QTcB (msec)	Dalbavancin (N = 81)						Comparator (N = 55)					
	1 dose n =26	%	2 dose n =55	%	Total n=81	%	7 days n =10	%	14 days n =45	%	Total n=55	%
QTcB > 500	0	-	2	3.6	**2**	**2.5**	0	-	1	2.2	**1**	**1.8**
♂: > 450 but <500	0	-	1	1.8	**1**	**1.2**	0	-	2	4.4	**2**	**3.6**
♀: > 470 but <500	0	-	2	3.6	**2**	**2.5**	0	-	0	-	0	-
Last 2 rows combined	0	-	3	5.5	**3**	**3.7**	0	-	3	6.7	**3**	**5.4**
♂ : QTcB:431-450	1	3.8	2	3.6	**3**	**3.7**	0	-	3	6.7	**3**	**5.4**
♀: QTcB: 451-470	0	-	1	1.8	**1**	**1.2**	0	-	2	4.4	**2**	**3.6**
Last 2 rows combined	1	3.8	3	5.5	**4**	**4.9**	0	-	5	11	**5**	**9.1**

QTcB Outliers

Table 13f: Shows the patients who had QTcB >500 msec and **table 13g** displays number of subjects with QTcB changes in studies 4 and 5.

Table 13f: Outlier table: Patients with QTcB or QTcF >500 msec in Studies 4 and 5

Subject PTID	Gender	Treatment received	Visit Day	QTcB	QTcF	Comments
		Dalbavancin 1 dose		-	-	None in this subgroup
04010005	Female	Dalbavancin 2 doses	Baseline Day 1	507 483	493 473	> 500msec at Baseline; no significant Δ on Rx
04005513	Male	Dalbavancin 2 doses	Baseline Day 1	498 507	484 482	QTcB > 500 msec on Day 1 (on Rx)
		Comparator 7 days		-	-	None in this subgroup
04010410	Female	Comparator 14 days	Baseline Day 1	485 506	458 444	> 500msec on Day 1

Table 13g: Patients with QTcB change in Studies 4 and 5

	Dalbavancin N = 356 (Screened)						Comparator N = 181 (Screened)					
	1 dose n =266	**%**	**2 doses n =90**	**%**	**Total n=356**	**%**	**7 days n =133**	**%**	**14 days n =48**	**%**	**Total n=181**	**%**
QTcB > 60 msec	0	-	0	-	**0**	**-**	0	-	0	-	**0**	**-**
QTcB >30 - 60 msec	2	0.8	2	2.2	**4**	**1.1**	0	-	1	2.1	**1**	0.6
QTcB <= 30 msec	3	1.1	27	30	**30**	8.4	2	1.5	23	47.9	**25**	13.8
Some subjects who had baseline ECG screening did not have a comparative ECG during Day 1 Treatment												

MO Comments: *Of the 2 dalbavancin-treated patients with QTcB reading > 500 msec in studies 4 and 5, one (04010005) was recorded at baseline. Subsequent reading following treatment with dalbavancin showed a QTcB reading of 483 msec. The second patient (04005513) was a 57 year-old male who received 2 doses of dalbavancin. His QTcB changed from a baseline value of 498 msec to 507 msec on day 1. His QTcB change from baseline was 9 msec. He had no relevant previous medical history and had a normal sinus rhythm with normal repolarization pattern. There were no QTcB changes > 500 msec. in studies 4 and 5.*

Phase 1 studies

There were no QTcB value > 500 msec in Phase 1 studies. And there were no QTc changes > 60 msec. One female subject who received > 1000 mg of dalbavancin had a QTcB change in the >30 - 60 msec category associated with a T wave amplitude decrease, which, though abnormal, was considered not clinically significant.

7.1.9.1 Analyses focused on measures of central tendency

Refer to Outlier's tables 13c (studies 8 and9) and Table 13f (Studies 4, 5 and 16).

7.1.9.3 Marked outliers and dropouts for ECG abnormalities

Refer to Outlier's tables 13c (studies 8 and9) and table 13f (Studies 4, 5 and 16) .
There were no dropouts for ECG abnormalities.

7.1.9.4 Additional analyses and explorations

No further suspicious safety ECG signals were available to necessitate or warrant additional analyses and exploration.

MO's comments: *Overall, ECG responses were similar across study arms. There were two dalbavancin-treated outliers with QTcB change > 60 msec from baseline. One from each arm had QTcB change in the 60s (msec). One dalbavancin-treated patient had the most significant QTcB change of 95 msec. She had atrial fibrillation, a poor R wave*

progression in precordial lead but with normal repolarization pattern. She had no bundle branch block. The ECG report described these events as an association of no qualitative drug effect. No further follow up information was available. These numbers were too few to make any ECG inferences in dalbavancin-treated patients. Animal data did not show any ECG (or QT) safety signal.

7.1.10 Immunogenicity

There are no human immunogenicity data available. Rat studies indicated that dalbavancin did not cause immunomodulation.

7.1.11 Human Carcinogenicity

There were no human carcinogenicity studies conducted, in humans or animals.

7.1.12 Special Safety Studies

There were no special safety studies conducted by the sponsor.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The potential for drug abuse with dalbavancin, per the sponsor, is considered to be low. No relevant studies investigating the dependence potential of dalbavancin in animals or humans were conducted.

Regarding withdrawal potential, the sponsor reported that the safety and tolerability were assessed from the start of treatment up to a follow-up visit. There was no evidence of a withdrawal or rebound effect on discontinuation of dalbavancin treatment.

7.1.14 Human Reproduction and Pregnancy Data

There were no human reproduction studies conducted. In study 9, pregnancy was reported in a patient (# 09025066) who received dalbavancin but who had a negative urine pregnancy test and was menstruating at baseline. According to the sponsor, the patient's serum pregnancy test result was found to be positive during infusion of the first dose of study medication. Study medication was then immediately discontinued. The patient received only 7.2 mL of the infusion. A repeat serum pregnancy test on Day 10 was negative and the patient was still menstruating. Because this positive serum pregnancy test was drawn at baseline prior to infusion of study drug, it was considered a baseline event and was not tabulated as an AE leading to withdrawal from study medication.

Animal data are however available in this area and reviewed by Dr. Wendy Schmidt as follows:

"The reproductive toxicity studies in rat and rabbit were adequate. The fertility index in

the rat was decreased at 45 mg/kg/day, while the NOAEL was 15 mg/kg/day. No embryotoxic or embryolethal effects were seen in the Segment II study in the rabbit at doses up to 15 mg/kg/day during organogenesis. In the rat, the fetal NOAEL was 15 mg/kg/day with delayed ossification in the sternebrae and skull. In the segment III rat study, increased lethality (stillborn/unexplained early death in 1st week) was seen at the HD (30 mg/kg/day to the dams). No effects no developmental milestones or the F2 generation were observed. The NOAEL was 15 mg/kg/day. Dalbavancin levels in both the pups' plasma and mothers' milk were approximately 1/10 of the maternal plasma levels of compound.
Dalbavancin was negative for mutagenicity and clastogenicity in the standard battery of assays. Dalbavancin was not irritating to skin or eyes and did not cause immunomodulation."

7.1.15 Assessment of Effect on Growth

No human data are available on the effect of dalbavancin on growth. In the animal data report available, it is reported that "In the rat, the fetal NOAEL was 15 mg/kg/day with delayed ossification in the sternebrae and skull. In the segment III rat study, increased lethality (stillborn/unexplained early death in 1st week) was seen at the HD (30 mg /kg /day to the dams). No effects on developmental milestones or the F2 generation were observed."

7.1.16 Overdose Experience

Patients who were potentially in situations to have dalbavancin overdose experience either received a high single dose or had dalbavancin doses administered too frequently. Such events occurred in the following instances:

- The highest single dose of dalbavancin administered was 1170 mg in study 4.

- An accidental dalbavancin overdose of 3000 mg administered within a 5-day period was reported for Patient 08-022-001.The sponsor reported that no changes in hepatic or renal laboratory values and no other potential signs of toxicity, including any other AEs, were observed.

The sponsor also added the following:

- Dose-limiting toxicity with dalbavancin has been not observed.

- Specific information is not available on the treatment of overdose with dalbavancin.

- Treatment of overdose with dalbavancin should consist of observation and general supportive measures.

- Subjects receiving hemodialysis (3 times/ week) have pharmacokinetic parameters similar to subjects with normal renal function.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The description of data sources used in this review was given under 7.1

7.2.1.2 Drug –Demographic Interaction

Demographic characteristics explored in conducting these trials included gender, age group (≥ 18 years), race/ethnicity (Caucasian, Black, Asian, Hispanic/Latino, other), and study location (Europe, North America) [Refer to table 3b and 3c]. No data were generated in children.

In overall AEs:
Females had more frequently reported AEs than males: 58.0% of dalbavancin-treated females compared with 47.9% of dalbavancin-treated males had at least 1 AE.

Older patients (≥65 years) had a greater frequency of AEs than younger patients (<65 years): of the patients who were ≥65 years in age who received dalbavancin, 60.9% had at least 1 AE whereas for the patients <65 years in age who received dalbavancin, 49.9% had at least 1 AE.

Patients treated in North America had greater frequencies of AEs than patients treated in Europe. Among patients treated in North America, 543 (59.7%) who received dalbavancin compared to 42 (19.4%) who received dalbavancin treatment in Europe had at least 1 AE.

Gastrointestinal disorders were the most common class of AEs for patients who were Caucasian, Black, and Asian. For patients who were Hispanic/Latino, the most common class of AEs was *investigations*, and for patients who were of other ethnicities, the most common class of AEs was *nervous system disorders*.

Extent of exposure (dose/duration)

Overall, 1267 patients received dalbavancin in all studies conducted. Out of these, 1045 were in comparative Phases 2 and 3 studies. Out of the 938 that were in the blinded controlled studies (8 and 9), 344 patients received 1 dose while 594 received 2 doses (refer to tables 1 and 2a). A total of 707 patients received 2 doses in the Phase 2 and Phase 3 studies. The reviewer considers these numbers adequate to enable assessments of the rates of common adverse events in dalbavancin-treated patients compared to comparator-treated patients.

In Phases 2 and 3, patients received one dose of 1000 mg (considered equivalent to 7 days of a comparator treatment), and, as needed, received a second dose of 500 mg (2 doses amounted to 14 days of the comparator treatment). The dosing of dalbavancin makes it unique among antibiotics. Its long half-life of 9-12 days, its pharmacodynamic profile, and the report of tissue accumulation for unknown but extended periods of time in animal data may be pointing to the fact that our knowledge of the entire safety profile of this NME, despite all the data reviewed in this submission, is probably still limited. Occasions may arise in the future that might cause clinicians to extend its use. New toxic effects might emerge that lie outside of the scope of our current knowledge, limited by the current duration of use.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The primary studies evaluated for adverse events were the blinded Phase 3 studies. Data from the other Phase 3 study (study 16, the open label comparative study) and Phase 2 studies (studies 4 and 5) were also to support the findings in the blinded studies. In addition, Phase 1 studies were examined for safety signals.

7.2.2.2 Postmarketing experience

Dalbavancin is a new drug product that has had no post-marketing experience anywhere at this time.

7.2.2.3 Literature

Literature review was an integral part of the review process and an essential review tool. It was important in the following ways:

1. It provided a source of information from which the reviewer could draw to get more familiar with any issue that may be contentious.
2. It allowed the reviewer to be more comfortable with a review assessment made, particularly if such assessment was in disagreement with that of the sponsor.

Literature was very helpful during the review of the outliers who had liver enzyme elevations.

In the case confounded by hepatitis C, the sponsor provided literature articles to argue the

points that:
a.) Nosocomial transmission of hepatitis C has been reported in the literature and
b.) liver enzyme elevation could be as high in acute hepatitis C as the patient developed on treatment (ALT 2525 IU/L).

The literature articles provided did not give information that was specific and strong enough to support the sponsor's position. The reviewer has not found an article that is specific and strong enough to counter the sponsor's assertion or position. The issue has remained unresolved.

In the second case, the sponsor made a diagnosis of alcoholic hepatitis that the reviewer disagreed with. The reviewer's comments can be seen just below table 9i. The literature articles cited are under references.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

In the animal toxicology review done by Dr. Wendelyn Schmidt, she reports the following:

"The reproductive toxicity studies in rat and rabbit were adequate. The fertility index in the rat was decreased at 45 mg/kg/day, while the NOAEL was 15 mg/kg/day. No embryotoxic or embryolethal effects were seen in the Segment II study in the rabbit at doses up to 15 mg/kg/day during organogenesis. In the rat, the fetal NOAEL was 15 mg/kg/day with delayed ossification in the sternebrae and skull. In the segment III rat study, increased lethality (stillborn/unexplained early death in 1st week) was seen at the HD (30 mg/kg/day to the dams). No effects no developmental milestones or the F2 generation were observed. The NOAEL was 15 mg/kg/day. Dalbavancin levels in both the pups' plasma and mothers' milk were approximately 1/10 of the maternal plasma levels of compound.

Dalbavancin was negative for mutagenicity and clastogenicity in the standard battery of assays. Dalbavancin was not irritating to skin or eyes and did not cause immunomodulation."

7.2.5 Adequacy of Routine Clinical Testing

ECG Testing

There were some important uncorrectable deficiencies in the data provided for review that limited the reviewer's ability to fully explore the contribution of the study drug to a particular abnormality revealed or partially detected because of methods employed in testing. For example, because of variability in ECG results, about 3 ECGs ought to be obtained and getting the mean reading each time at baseline, on-treatment and post treatment (because of the long half life of dalbavancin). Such ECG readings should have

been more informative. ECGs in the studies submitted were conducted by obtaining one at baseline and the second on Day 1. ECGs done in isolation have the potential to miss some important cardiac signals unless conducted in the manner suggested and would be helpful in increasing positive and negative predictive values.

Also refer to **7.3** [Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions] for related discussion.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Four studies were conducted to evaluate induction, inhibition, and metabolism. Two of the studies were considered adequate by the Clinical Pharmacology reviewer. The other two studies were noted to have limitations (see complete Clinical Pharmacology review by Dr. Charles Bonapace).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Most parts of the process were adequate. The follow up of abnormal laboratory results was not as adequate. The evaluations of patients with extremely abnormal laboratory values were inadequate. The conduction of ECGs on study patients were less than adequate.

7.2.8 Assessment of Quality and Completeness of Data

On balance, the data submitted represented substantial evidence of safety. There were however some patients for whom safety data collection was sub-optimal. In such patients, more rigorous data collection would facilitate assessment of causality.

7.2.9 Additional Submissions, Including Safety Update

While the reviewer is not asking for additional submissions at this time, it is important that vigilance is maintained to enhance the detection of any safety signal during post market surveillance.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most common dalbavancin–related adverse events were from the gastrointestinal (GI) system, i.e. nausea, diarrhea and vomiting. Headache and non-specific abdominal pain were also reported. The frequencies of these GI symptoms were comparable with those seen in the comparator- treated patients. These events were mostly mild, and much fewer numbers were moderate in severity. Rash (unspecified) was the most common AE leading to the discontinuation of dalbavancin. Two cases of leukopenia were the only

drug-related SAEs. One resolved by the TOC visit (Day 29). There was no follow up information on the second.

There were liver enzyme abnormalities occurring with similar frequencies in both dalbavancin-treated and comparator- treated patients. But the 3 outliers with enzyme abnormalities > 20x ULN all received dalbavancin treatment and none received comparator-treatment. Two of the 3 were confounded.

Additional information either in future trials for, perhaps other indications, or data from post-marketing surveillance should improve our understanding of the contribution of this drug, or lack thereof, to hepatic enzyme elevations.

Five patients developed hypoglycemia in the dalbavancin-treated arm compared to none in the comparator- treated arm. One case was confounded by diabetes mellitus. The overall number was small. Nevertheless, the event is noteworthy.

Hyperglycemia cases were also more among the dalbavancin-treated than among the comparator- treated patients. Four out of six patients were confounded by diabetes mellitus. The numbers were also small. Given the vacuolization, degeneration and apoptosis of pancreatic acinar cells in animals treated with dalbavancin, hyperglycemia is also noteworthy despite the confounding role of diabetes mellitus in these patients.

One dalbavancin-treated patient had a QTcB change of 95 msec. The ECG was not repeated. The significance of this is uncertain at this time.

These concerns, as they meet the criteria of frequency and relevance, should be reflected in the label pending future information to reinforce, confirm or refute what we know or suspect at this time.

Important Limitations of Data

There were some important deficiencies in the data provided for review. These deficiencies limited the reviewer's ability to ascertain the contribution of the study drug to particular abnormalities revealed or reported. Such deficiencies included the following:

1. ECG testing.

An example of this is the inadequacy in ECG testing. ECGs in the studies submitted were conducted by obtaining one before drug administration (baseline) and the second after drug administration, supposedly around C_{max}. The paired ECG data were usually obtained around the infusion of medication. Many abnormal baseline QTc recordings were obtained. Given the general variability in ECG results, about 3 ECGs readings ought to be obtained for each patient at baseline to obtain a mean of the 3 readings. In addition, on-treatment and post treatment (because of the long half life of dalbavancin) readings should have been more informative. ECGs done in isolation have the potential to miss some important cardiac signals. ECGs conducted in the manner suggested above would be helpful in increasing positive and negative predictive values.

2. Patient evaluation.

An example of this is the outlier hepatobiliary abnormality which the investigator and sponsor diagnosed as alcoholic hepatitis. The presentation of the patient, the degree and

pattern of ALT/AST abnormalities were not considered common in alcoholic hepatitis. More importantly, the investigator did not rule out other possibilities to enable a more an assessment of whether the study drug contributed to, or perhaps, caused, the liver injury that resulted in hepatic enzyme abnormalities.

3. Follow-up Strategy
There were patients that moved away from study sites and could not be reached. However, there were some patients with whom the investigators may have had contact (e.g. patients 09005026 or 09005078) that had abnormal laboratory values that needed repeated or follow up values. Some of these were not pursued to ascertain time to resolution of their laboratory abnormalities. In some cases, the sponsor reported the investigator as saying subsequent values were resolving without documented evidence (e.g. patient 08-220-001).

4. The reviewer had reservations about the conclusions the sponsor reached with respect to the diagnoses of some of their cases. An example was the case of alcoholic hepatitis case made above (patient # 08206017). Given the clinical presentation and the enzyme transition profile, all literature the reviewer has read about the topic is in disagreement. If the patient had been properly evaluated by the investigators and the sponsors they probably would have come to a different conclusion.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The individual studies from which data were pooled for the various analyses done are as follows:

Phase 1
Received dalbavancin = 141 subjects (3 received 3 extra doses in study 11).
Received Placebo = 19 patients

Four studies in healthy subjects (Studies 1, 2, 10 and 19)
Three studies in special populations:
27 Subjects with impaired hepatic status (Study 12)
43 Subjects with impaired renal status (Studies 3, 11 and 13)
In study 3, only 3 subjects received Dalbavancin each at a single dose of 70 mg. The sponsor prematurely terminated the study to proceed to a higher more clinically relevant dose.

Studies 1 and 2 (Phase 1) had Placebo Arms.

Phase 2: Open label comparative studies:
Received dalbavancin = 81 patients
Received comparator = 55 patients
One study invloved patients with catheter-related bloodstream infection (BSI) (VER001-4)
The second study was in patients with complicated SSSI (cSSSI) (VER001-5)

Phase 3: Double-blinded comparative studies = VER001-8 and VER001-9
Open label comparative study = VER001-16

Received dalbavancin = 1045 patients
Received comparator = 518 patients

1. Double-blinded study in patients with Uncomplicated SSSI (uSSSI) (Study 8)
2. Double-blinded study in patients with complicated SSSI (cSSSI) (Study 9)
3. Open label, comparative study included patients with MRSA in both uSSSI and cSSSI (Study 16)

7.4.1.2 Combining data

Combining Studies for Analyses

For proper analyses and comparisons of study results, the studies in this submission were re-grouped, according to study design. Double-blinded studies were grouped together (studies 8 and 9), as were open-label studies (studies 4, 5, and 16). Phase 1 studies were evaluated separately. We later requested the sponsor to recreate some tables in this manner to facilitate the review process. Old tables were used, as relevant, if the information sought was unaffected by study grouping. Grouping of studies were in the order given below. Combining studies of similar design allowed for reliable analyses of differences in safety signals across study arms. The combinations were as follows:

Randomized, double-blind, multi-center studies: Protocols 8 and 9
Randomized , open-label, multi-center studies: Protocols 4, 5 and 16
Phase 1 Studies

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dose-dependent AEs were not apparent in the various explorations for safety signals. Glucose metabolism is one area where the number of patients who received 2 doses of dalbavancin had more hypoglycemia and hyperglycemia than patients who received one dose or the comparator. Most of the hyperglycemia patients had diabetes mellitus. One of

the hypoglycemia patients was also diabetic. More importantly, because the number of the patients was small (refer to table 10g.2 and 10i on page 98) no firm conclusions could be drawn.

7.4.2.2 Explorations for time dependency for adverse findings

In this review, those patients who received either 2 doses of dalbavancin (or 14 days of the comparator) were exposed more to the drug compared to patients who received 1 dose of dalbavancin (or 7 days of comparator).

7.4.2.3 Explorations for drug-demographic interactions

Refer to the discussion under Drug-Demographic (Section7.2.1.2) above

7.4.2.4 Explorations for drug-disease interactions (and dalbavancin in specific disease populations)

The sponsor analyzed AEs by disease.

Hepatic Impairment

Among Phase 2/3 patients, AEs were reported more frequently in patients who had elevated baseline hepatobiliary (BH) values than those who did not.

Elevation of BH status was determined based on the following:

1. Baseline ALT or AST > 3 x the ULN, or
2. Baseline alkaline phosphatase level > greater 1.5 times the ULN.

Forty three (4.1%) dalbavancin-treated patients and 37 (7.0%) comparator-treated patients had elevated BH values. Among these, 33 (76.7%) dalbavancin-treated patients and 26 (70.3%) comparator-treated patients had at least 1 AE whereas, for patients with no elevated BH values, 511 (50.8%) dalbavancin-treated patients and 278 (56.4%) comparator-treated patients had at least 1 AE.

Gastrointestinal disorders (GID) were the most commonly reported AEs for all patients, more so in patients with elevated BH values in whom 32.6% of dalbavancin-treated patients and 35.1% of comparator-treated patients had at least 1 GID. Among patients with non-elevated BH values, 18.4% of dalbavancin-treated patients and 21.9% of comparator-treated patients had at least 1 GID.

The most frequently occurring AEs (≥5%) among dalbavancin versus comparator-treated patients with elevated BH values were diarrhea (14.0% vs 2.7%), vomiting (14.0% vs 10.8%), nausea (11.6% vs 5.4%), abdominal pain (9.3% vs 0%), constipation (9.3% vs

8.1%), insomnia (4.7% vs 8.1%), anemia (4.7% vs 5.4%), hypokalemia (4.7% vs 5.4%), oral candidiasis (2.3% vs 8.1%), back pain (2.3% vs 5.4%), headache (2.3% vs 5.4%), and pain in limb (2.3% vs 5.4%). Others included deep venous thrombosis, fungal rash, gamma-glutamyltransferase increased, hypoaesthesia, pneumonia, pruritis, and urinary tract infection.
The only AEs that occurred in ≥5% of dalbavancin or comparator-treated patients with non-elevated baseline hepatobiliary values were nausea (5.8% vs 8.5%), headache (4.9% vs 6.1%), and diarrhea (4.8% vs 6.9%).

The Phase 1, Study 12, an open-label study, evaluated the safety of dalbavancin in subjects with mild, moderate, and severe hepatic impairment as well as in healthy subjects with normal hepatic function.
Among the 27 subjects enrolled, 6 had mild, 6 moderate, and 5 severe hepatic impairment; 10 had normal hepatic function. All but one subject (discontinued study drug at the request of the subject or investigator) received dalbavancin.
Overall, dalbavancin was well tolerated in subjects with mild to moderate hepatic impairment. There was no increase in incidence, severity, or relationship of AEs observed with dalbavancin administration in subjects with mild to moderate hepatic impairment compared with subjects with normal hepatic function. Transient increases in liver function tests with dalbavancin administration were comparable between subjects with hepatic impairment and those with normal hepatic function.

Renal Impairment

According to the sponsor, among the Phase 2/3 patients, 24 (2.1%) dalbavancin-treated patients and 22 (3.8%) comparator-treated patients had baseline creatinine clearance (BCC) <50 mL/min; 187 (16.6%) dalbavancin-treated patients and 92 (16.1%) comparator-treated patients had BCC between 50 to <80 mL/min; 911 (80.9%) dalbavancin-treated patients and 454 (79.2%) comparator-treated patients had BCC ≥80 mL/min (see table 14b).

As the sample size is small for patients with BCC <50 mL/min, there were no sufficient data to make meaningful comparisons by baseline renal impairment.
Among patients with BCC of <50 mL/min, 14 (58.3%) dalbavancin-treated patients and 13 (59.1%) comparator-treated patients had at least 1 AE. Among patients with BCC of 50 to <80 mL/min, 109 (58.3%) dalbavancin-treated patients and 58 (63.0%) comparator-treated patients had at least 1 AE. Among patients with BCC ≥80 mL/min, 458 (50.3%) dalbavancin-treated patients and 254 (55.9%) comparator-treated patients had at least 1 AE.

Gastrointestinal disorders were the most commonly reported AEs for patients with BCC between 50 to <80 mL/min and ≥80 mL/min. For patients with BCC of <50 mL/min, infections and infestations were the most commonly reported types of AEs. Among patients with creatinine clearance <50 mL/min, 4 (16.7%) dalbavancin-treated patients and 8 (36.4%) comparator-treated patients had at least 1 AE in the system organ class of infections and infestations. Among patients with creatinine clearance of 50 to <80

mL/min, 34 (18.2%) dalbavancin-treated patients and 14 (15.2%) comparator-treated patients had at least 1 AE in the system organ class of infections and infestations. Among patients with creatinine clearance of ≥80 mL/min, 115 (12.6%) dalbavancin-treated patients and 73 (16.1%) comparator-treated patients had at least 1 AE in the system organ class of infections and infestations.

The lower part of table 14a displays the individual AEs (≥ 5% or < 5%) in the various creatinine clearance categories . Of note, one dalbavancin-treated patient had severe nausea, 2 dalbavancin-treated patients had severe diarrhea, and 4 dalbavancin-treated patients had severe headache.

Table 14 a: AEs in Phase 2 and 3 Patients at different levels of creatinine clearance

	Dalbavancin			**Comparator**		
	Creatinine Clearance (mL/min.)			**Creatinine Clearance (mL/min.)**		
	≥80	**50 to <80**	**<50**	**≥80**	**50 to <80**	**<50**
N (%) →	911 (80.9)	187 (16.6)	24 (2.1)	454 (79.2)	92 (16.1)	22 (3.8)
At least 1 AE	458 50.3)	109 (58.3)	14 (58.3)	254 (55.9)	58 (63.0)	13 (59.1)
AE Types	**≥80**	**50 to <80**	**<50**	**≥80**	**50 to <80**	**<50**
% Nausea	5.8	8.6	<5	7.7	9.8	13.6
% Diarrhea	5.4	5.9	8.3	6.2	9.8	<5
% Vomiting	<5	<5	8.3	<5	<5	13.6
% Phlebitis	<5	<5	8.3	<5	<5	<5
% UTI	<5	5.9	<5	<5	<5	<5
% Headache	5.4	<5	<5	5.5	<5	<5

Treatment-Related Adverse Events in Phase 2/3 patients

For patients having BCC <50 mL/min, 6 (25.0%) dalbavancin-treated patients and 6 (27.3%) comparator-treated patients had at least 1 treatment-related AE. Among patients with BCC of 50 to <80 mL/min, 33 (17.6%) dalbavancin-treated patients and 36 (39.1%) comparator-treated patients had at least 1 treatment-related AE. Among patients with BCC ≥80 mL/min, 207 (22.7%) dalbavancin-treated patients and 115 (25.3%) comparator-treated patients had at least 1 treatment-related AE.

Specific Treatment –related AEs
All treatment-related AEs that occurred in dalbavancin-treated patients with BCC <50 mL/min were reported in 1 patient each and included increased blood uric acid, candidal infection, diarrhea, frequent bowel movements, headache, mucosal inflammation, phlebitis, generalized rash, superficial thrombophlebitis, and vomiting; none of these events was severe in intensity

Dalbavancin-treated patients
Among dalbavancin-treated, summarized in table (table 14 b**),** patients with creatinine clearance of 50 to <80 mL/min, treatment-related AEs that occurred in ≥ 1% of

dalbavancin-treated patients (overall) included nausea (5 patients, 2.7%); rash (4 patients, 2.1%); diarrhea, dizziness, and fungal vaginosis (3 patients each, 1.6%); and increased gamma-glutamyl-transferase, headache, and phlebitis (2 patients each, 1.1%); none of these events was severe in intensity.
Among dalbavancin-treated patients with creatinine clearance of ≥80 mL/min, treatment-related AEs that occurred in ≥1% of dalbavancin-treated patients (overall) were diarrhea (3.2%), nausea (3.0%), increased gamma-glutamyl-transferase (1.4%), increased blood lactate dehydrogenase (1.3%), vomiting (1.3%), rash (1.3%), and headache (1.3%); of these, 1 patient.s headache was severe in intensity.

Comparator-treated patients
Among comparator-treated patients, the most frequently occurring treatment-related AE for patients with baseline creatinine <50 mL/min was candidal infection, reported by 2 (9.1%) patients; all other events were reported by 1 patient each. Among comparator-treated patients with baseline creatinine of 50 to <80 mL/min, the most frequently occurring treatment-related AEs were diarrhea (5.4%), nausea (4.3%), and thrombocytopenia (4.3%). Among comparator-treated patients with baseline creatinine of ≥ 80 mL/min, the most frequently occurring treatment-related AEs were diarrhea (3.5%) and nausea (3.5%).

Table 14 b: Treatment –related AEs in Phase 2 and 3 Patients at different levels of creatinine clearance

	Dalbavancin			**Comparator**		
	Creatinine Clearance (mL/min.)			**Creatinine Clearance (mL/min.)**		
	≥80	**50 to <80**	**<50**	**≥80**	**50 to <80**	**<50**
N (%)	911(80.9)	187(16.6)	24 (2.1)	454 (79.2)	92 (16.1)	22 (3.8)
≥ 1 Rx-related AE	207 (22.7%)	33 (17.6%)	207 (22.7%)	115 (25.3%)	36 (39.1%)	6 (27.3%)
	Dalbavancin			**Comparator**		
	Creatinine Clearance (mL/min.)			**Creatinine Clearance (mL/min.)**		
AE Types	**≥80**	**50 to <80**	**<50**	**≥80**	**50 to <80**	**<50**
Nausea	27 (3.0%)	5 (2.7%)	< 1%	16 (3.5%)	5 (5.4%)	1 (4.5%)
Diarrhea	29 (3.2%)	3 (1.6)	1 (4.2 %)	16 (3.5%)	4 (4.3%)	1 (4.5%)
Vomiting	12 (1.3%)	< 1%	1 (4.2 %)	< 1%	< 1%	1 (4.5%)
Phlebitis	< 1%	< 1%	< 1%	< 1%	< 1%	1 (4.5%)
UTI	< 1%	< 1%	< 1%	< 1%	< 1%	1 (4.5%)
Headache	12 (1.3%)	2 (1.1%)	< 1%	< 1%	< 1%	1 (4.5%)
↑ uric acid	< 1%	< 1%	1(4.2 %)	< 1%	< 1%	1 (4.5%)
Bowel frequency	< 1%	< 1%	1(4.2 %)	< 1%	< 1%	1 (4.5%)
Candidal Infection Nos	< 1%	< 1%	1(4.2 %)	< 1%	< 1%	2 (9.1%)
Generalized rash	12 (1.3%)	4 (2.1%)	1(4.2 %)	< 1%	< 1%	1 (4.5%)
Phlebitis	< 1%	2 (1.1%)	< 1%	< 1%	< 1%	1 (4.5%)
Thrombophlebitis	< 1%	< 1%	< 1%	< 1%	< 1%	1 (4.5%)
Dizziness	< 1%	3 (1.6)	< 1%	< 1%	< 1%	1 (4.5%)
Fungal Vaginosis	< 1%	3 (1.6)	< 1%	< 1%	< 1%	1 (4.5%)
↑ GGT	13 (1.4)	2 (1.1%)	< 1%	< 1%	< 1%	1 (4.5%)
↑ LDH	12 (1.3%)	< 1%	< 1%	< 1%	< 1%	1 (4.5%)

Phase 2/3 Treatment-Related AEs Leading to Discontinuation of Study Drug

Among patients with BCC <50 mL /min, 1 (4.2%) dalbavancin-treated patient had treatment-related AE that led to discontinuation of study drug compared to none of comparator-treated patients. Among patients with BCC between 50 and <80 mL/min, no dalbavancin-treated patient, and 1 (1.1%) comparator-treated patient had a treatment-related AE that led to discontinuation of study drug. Among patients with baseline creatinine clearance ≥80 mL/min, 13 (1.4%) dalbavancin-treated patients and 11 (2.4%) comparator-treated patients had at least 1 treatment-related AE that led to discontinuation of study drug.

MO Comments: *Dalbavancin appeared to have been well tolerated in patients with renal impairment, given the low incidence of treatment-related AEs leading to study drug discontinuation.*

Phase 2/3 Laboratory Results

No trends were observed in patients with impaired renal function or with potentially clinically significant changes in laboratory results.

Disease Indication

An overall summary of AEs by disease indication are given in Appendix 14

Catheter-Related Blood Stream Infection (CRBSI)

- Patients in study 4 with Catheter-Related Blood Stream Infection (CRBSI) had the highest incidence of AEs. One hundred percent of dalbavancin-treated patients and 91.2% of comparator-treated patients with CRBSI had at least 1 AE (**Table 14 c)**.

- Of the patients with CRBSI, 13 (32.5%) of dalbavancin-treated patients had at least 1 treatment-related AE compared with 6 (17.6%) comparator-treated patients.

- The system organ class most commonly affected by treatment-related AEs was gastrointestinal disorders.

- No dalbavancin-treated patient had a treatment-related AE that led to discontinuation of study drug whereas 1 (2.9%) comparator-treated patient had treatment-related AEs that led to discontinuation of study drug (acute renal failure and renal impairment).

Table 14 c: Patients in Study 4 (CRBSI)

	Dalbavancin	Comparator
At least 1 AE	100%	91.2%
Rx –related AE	13 (32.5%)	6 (17.6%)
Rx –related AE leading to study drug discontinuation	0	1 (2.9%)
AE types included nausea diarrhea		

uSSSI

- Among patients with uSSSI, 40.3% of dalbavancin-treated patients and 40.1% of comparator-treated patients had at least 1 AE. (table 14 d)
- Of the patients with uSSSI, 68 (15.3%) dalbavancin-treated patients had at least 1 treatment-related AE compared with 39 (18.0%) comparator-treated patients
- Six (1.4%) dalbavancin-treated patients and 5 (2.3%) comparator-treated patients had at least 1 treatment-related AE that led to discontinuation of study drug.
- Gastrointestinal disorders were the most common class of AEs for uSSSI
- For comparator-treated patients, the most frequently occurring treatment-related AE that led to discontinuation of study drug was nausea, reported by 3 (1.4%) comparator-treated patients; all 3 received 7 days of treatment. Treatment-related nausea led to discontinuation of study drug for 1 (0.2%) dalbavancin-treated patient with uSSSI.

Table 14 d: Phase 2/3 Patients with uSSSI

	Dalbavancin	Comparator
At least 1 AE	40.3%	40.1 %
Rx –related AE	15.3 %	18.0%
Rx –related AE leading to study drug discontinuation	6 (1.4%)	5 (2.3%)
AE types included nausea and diarrhea		

cSSSI

- Among patients with cSSSI, 57.0% of dalbavancin-treated patients and 64.6% of comparator-treated patients had at least 1 AE (table 14e)

- In this group of patients, 167 (26.0%) dalbavancin-treated had at least 1 treatment-related AE compared with 112 (34.8%) of comparator-treated patients.

- Eight (1.2%) dalbavancin-treated patients and 6 (1.9%) comparator-treated patients had at least 1 treatment-related AE that led to discontinuation of study drug.

- Gastrointestinal disorders were the most common class of AEs for cSSSI

- The most frequently occurring treatment-related AE that led to discontinuation of study drug for patients with cSSSI was rash, reported by 0.6% of both dalbavancin- and comparator-treated patients.

Table 14 e cSSSI

CSSSI	**Dalbavancin**	**Comparator**
At least 1 AE	57%	64.6 %
Rx –related AE	167 (26.0%)	112 (34.8%)
Rx –related AE leading to study drug discontinuation	8 (1.2%)	6 (1.9%)
AEs included diarrhea and rash in patients who received dalbavancin		

Phase 2/3 Laboratory Results

In general, patients with cSSSI more frequently had PCS laboratory results that were also PCS changes from baseline than patients with uSSSI.
Very few patients with CRBSI had PCS laboratory values or changes from baseline, and due to the small sample size of this subgroup, no definitive analyses were possible on trends in this indication.

7.4.2.5 Explorations for drug-drug interactions

The sponsor examined the potential for drug-drug interactions in patients in Phase 2/3 integrated database by determining the proportions of these patients who had AEs after

receiving concomitant medications of special interest (i.e. aztreonam, aminoglycosides, warfarin, and statins).

The relationship of the AE start date to the start date of the concomitant medication was examined. AEs beginning on or after the start date of the concomitant medication were considered to have occurred during treatment regardless of the stop date of the concomitant medication.

A total of 124 dalbavancin-treated patients and 63 comparator-treated patients were taking aztreonam. Of these, 83 (66.9%) dalbavancin-treated patients and 49 (77.8%) comparator-treated patients had at least 1 AE on aztreonam [see table 14f, below].

The most frequently reported AEs in dalbavancin-treated group were diarrhea (1.2%); anemia (0.9%); vomiting (0.8%); and nausea, constipation, hypomagnesemia, and insomnia (each reported by 0.7% of patients). Among comparator-treated patients who were taking aztreonam, the most frequently reported AEs were nausea (1.4%), constipation and loose stools (each reported by 1.0% of patients).

A total of 22 dalbavancin-treated patients and 18 comparator-treated patients were taking aminoglycosides. Of these, 14 (63.6%) dalbavancin-treated patients and 9 (50.0%) comparator-treated patients had at least 1 AE while using aminoglycosides. Among dalbavancin-treated patients who were taking aminoglycosides, the most frequently reported AEs were insomnia, vomiting, and anemia, each reported by 3 (0.3%) of patients. Among comparator-treated patients who were taking aminoglycosides, the most frequently reported AEs were insomnia, hypokalemia, nausea, peripheral edema, constipation, depression, fatigue, and urinary tract infection, each reported by 2 (0.3%) of patients.

A total of 51 dalbavancin-treated patients and 19 comparator-treated patients were taking warfarin. Of these, 38 (74.5%) dalbavancin-treated patients and 16 (84.2%) comparator-treated patients had at least 1 AE while using warfarin. Among the dalbavancin-treated patients on warfarin, the most frequently reported AE was nausea, reported by 7 (0.6%) of the patients. Among comparator-treated patients on warfarin, the most frequently reported AE was thrombocytopenia, reported by 3 (0.5%) of the patients.

A total of 151 dalbavancin-treated patients and 56 comparator-treated patients were taking statins. Of these, 106 (70.2%) dalbavancin-treated patients and 40 (71.4%) comparator-treated patients had at least 1 AE while using statins (Appendix 2.7.4.A, Table 8.3.4). Among dalbavancin-treated patients who were taking statins, the most frequently reported AEs were constipation (1.0%); and nausea, headache, and pruritus (each reported by 0.9% of patients). Among comparator-treated patients who were taking statins, the most frequently reported AEs were diarrhea and hypoglycemia (0.7% of patients each); and constipation, hyperkalemia, increased blood lactate dehydrogenase, infusion site pain, peripheral edema, dysgeusia, and thrombocytopenia (0.5% of patients each).

In vitro studies conducted to evaluate the potential for dalbavancin to interact with the major human cytochrome P-450 isoforms showed that dalbavancin is neither an inhibitor, an inducer of or a substrate for any of the isoforms (i.e., CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) was not reported.

Table 14 f Drug –Drug Interaction

Concomitant Drug	***Dalbavancin RX group***	***# (%) of Patents with AE***	***Most common AE***	***Comparator RX group***	***# (%) of Patents with AE***	***Most common AE***
	N	***n (%)***		***N***	***n (%)***	
Aztreonam	*124*	*83(66.9%)*	*diarrhea*	*63*	*49 (77.8%)*	*nausea*
Aminoglycosides	*22*	*14 (63.6%)*	*insomnia*	*18*	*9 (50.0%)*	*insomnia*
Warfarin	*51*	38 (74.5%)	nausea	*19*	16 (84.2%)	*↓ Platelet*

7.4.3 Causality Determination

Adverse events (deaths, serious adverse events, common adverse events and uncommon adverse events) were assessed to determine the relationship of the events to the receipt of dalbavancin. These were done by evaluating the AE(s) in subjects or patients in groups, subgroups or individually, depending on the analysis or analyses being done. It involved comparisons of dalbavancin-treated patients with comparator-treated patients, exploring differences in frequencies of AEs or trends in abnormalities; or differences in subgroup AEs for possible dose-related AEs; or individually, e.g. patients who were outliers for specific abnormalities, drug-emergent AEs, dropouts or deaths.
In the submitted data, the frequencies of AEs, SAEs and deaths were similar between the dalbavancin-treated patients and comparator-treated patients. There were outliers in hepatobiliary abnormalities involving ALT/AST elevation > 20x upper limit of normal involving dalbavancin-treated patients. There were also more abnormalities in glucose homeostasis (with cases of hypoglycemia and hyperglycemia) in dalbavancin –treated patients. Whether dalbavancin caused or contributed to the development of these abnormalities were suspected but could not be definitely determined.

9 OVERALL ASSESSMENT

9.1 MO's Final Safety Conclusions

Based on the analyses of the data reviewed, the Medical Reviewer is able to make the following safety conclusions:
The most common toxicities in dalbavancin-treated patients were related to the gastrointestinal (GI) tract: nausea, diarrhea, vomiting and constipation. These adverse events in dalbavancin-treated patients occurred at frequencies that were similar to the patients who received comparator. They were mostly mild to moderate in severity, and resolved within a median duration of 3 days.

Headache and pyrexia occurred with comparable frequencies in the two treatment arms. They were also mild to moderate in severity and generally resolved within about 3 days

Of the deaths that occurred in patients who received dalbavancin, none appeared to be causally associated with the receipt of dalbavancin. The rates of deaths in those who received comparator were similar.

The rates of serious adverse events (SAEs) in patients that received dalbavancin were also similar to the rates in patients who were comparator-treated. Aside from one case of leukopenia which resolved within 29 days, no other causal relationship could be determined between the receipt of dalbavancin and any other SAE.

The rates of serious adverse events (SAEs) in patients that received dalbavancin were also similar to the rates in patients who were comparator-treated. Aside from one case of leukopenia which resolved within 29 days, no other causal relationship could be determined between the receipt of dalbavancin and any other SAE.

Laboratory Data

Toxicology study review for this NDA reported the following toxic effects in rats and dogs that received dalbavancin for up to 3 months duration:

- Persistent liver enzyme (AST/ALT) elevations
- Hepatocellular necrosis/ vacuolization/degeneration
- Pancreatic (acinar cells) vacuolization/degeneration/ apoptosis
- Persistent elevations in Blood Urea Nitrogen (BUN)
- Renal tubular vacuolization/degeneration/ necrosis

And the following affected dogs only:

- Persistent RBC decreases (up to one year post-dose)

In the safety database, the following laboratory abnormalities were noted:

1. **Liver**

   Although the rates of ALT/ AST elevations < 20 x Upper Limit of Normal (ULN) were comparable across study arms, the contribution of dalbavancin to liver enzyme elevations >20 x ULN could not be excluded in two cases.

2. **Pancreas**

Hypoglycemia

Five dalbavancin-treated patients in studies 8 and 9, one of whom was diabetic, developed clinically significant hypoglycemia (i.e., glucose level of < 40 mg/dL). They were reported to be asymptomatic. By comparison, no patient who received

comparator treatment in the same studies developed hypoglycemia. Two patients in Phase 1 also developed clinically significant hypoglycemia.

Hyperglycemia

Six dalbavancin-treated patients had hyperglycemia compared to one comparator-treated patient in studies 8 and 9. However, four of the six dalbavancin-treated patients with hyperglycemia were diabetic. In addition, three other hyperglycemic cases were found with one case in each of Studies 16 (Phase 3), 5 (Phase 2), and 11 (Phase 1). These numbers are too small to enable assessment of their clinical significance. The issue is also confounded by the presence of diabetes mellitus. Although the animal pancreatic toxicity did not involve the islet cells, these findings are noteworthy. There were no amylase or lipase results in the database.

3. **Kidney**

There were no safety signals detected at this time in the data reviewed. The elevations in BUN and creatinine were comparable across study arms. No outliers in these laboratory parameters were seen at this time.

4. Hematology

The frequencies of anemia were similar across study arms. No outliers or abnormal trends were found.

There were a few QTcB abnormalities, including one notable outlier who received dalbavancin and had a post baseline QTcB of 95 msec. The test was never repeated and therefore it remains unknown if the abnormality was clinically significant.

The safety implications of prolonged or repeated use of dalbavancin could not be evaluated in this review. Post marketing surveillance may provide useful information in this area.

The relatively small size of this database (in the order of one thousand) could have limited the reviewer's ability to detect rare adverse events. Although the overall population may have been acceptable for this review, a larger size of study population may have allowed for a fuller and more comprehensive characterization of the safety profile of dalbavancin. Post-marketing surveillance may provide such additional information.
In summary, the sponsor has demonstrated an acceptable safety profile for dalbavancin for the indication of cSSSI for which efficacy has been demonstrated. The safety profile is adequate to support approval. However, satisfactory post marketing surveillance is advised to detect any possible safety signal not apparent in this database.

The sponsor has also demonstrated that, when used for the treatment of cSSSI, the safety profile of dalbavancin is similar to that of the comparators used in the clinical studies.

10 APPENDICES

Additional Safety Tables are included in this section

APPENDIX 10.1

Table ISS SAE 89- 2 Serious Adverse Events by Decreasing Frequency in Studies 8 and 9 subjects

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
NECROTISING FASCIITIS NOS	1 (0.3)	0	1 (0.1)	0	1 (0.3)	1 (0.2)
ANGINA PECTORIS	0	1 (0.2)	1 (0.1)	0	0	0
ATRIAL FIBRILLATION	1 (0.3)	0	1 (0.1)	0	0	0
BRONCHITIS NOS	0	1 (0.2)	1 (0.1)	0	0	0
CARDIAC DEATH	1 (0.3)	0	1 (0.1)	0	0	0
CARDIOGENIC SHOCK	1 (0.3)	0	1 (0.1)	0	0	0
CARDIOPULMONARY FAILURE	1 (0.3)	0	1 (0.1)	0	0	0
CHEST PAIN	1 (0.3)	0	1 (0.1)	0	0	0
DIABETES MELLITUS INADEQUATE CONTROL	0	1 (0.2)	1 (0.1)	0	0	0
DYSPNOEA	0	1 (0.2)	1 (0.1)	0	0	0
FALL	0	1 (0.2)	1 (0.1)	0	0	0
FURUNCLE	0	1 (0.2)	1 (0.1)	0	0	0
GASTROINTESTINAL HAEMORRHAGE NOS	1 (0.3)	0	1 (0.1)	0	0	0
HEPATIC NEOPLASM NOS	0	1 (0.2)	1 (0.1)	0	0	0
HIP FRACTURE	0	1 (0.2)	1 (0.1)	0	0	0
LEUKOCYTOSIS	0	1 (0.2)	1 (0.1)	0	0	0
MEDICATION ERROR	1 (0.3)	0	1 (0.1)	0	0	0
METASTATIC NEOPLASM NOS, PRIMARY SITE UNKNOWN	0	1 (0.2)	1 (0.1)	0	0	0

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment.
Patients are only counted once at each level of summarization.

APPENDIX 10.1

Table ISS SAE 89- 3 Serious Adverse Events by Decreasing Frequency in Studies 8 and 9 subjects (continued)

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
MYOCARDIAL INFARCTION	0	1 (0.2)	1 (0.1)	0	0	0
MYOCLONUS	0	1 (0.2)	1 (0.1)	0	0	0
NEPHROLITHIASIS	1 (0.3)	0	1 (0.1)	0	0	0
NON-HODGKIN'S LYMPHOMA NOS	1 (0.3)	0	1 (0.1)	0	0	0
PAIN IN EXTREMITY	0	1 (0.2)	1 (0.1)	0	0	0
PERIPHERAL OCCLUSIVE DISEASE	0	1 (0.2)	1 (0.1)	0	0	0
RECTAL ABSCESS	0	1 (0.2)	1 (0.1)	0	0	0
RENAL FAILURE NOS	1 (0.3)	0	1 (0.1)	0	0	0
RENAL FUNCTION TESTS NOS ABNORMAL	1 (0.3)	0	1 (0.1)	0	0	0
SLEEP APNOEA SYNDROME	1 (0.3)	0	1 (0.1)	0	0	0
THERAPEUTIC AGENT POISONING	0	1 (0.2)	1 (0.1)	0	0	0
VIRAL INFECTION NOS	0	1 (0.2)	1 (0.1)	0	0	0
WOUND INFECTION	0	1 (0.2)	1 (0.1)	0	0	0
ABDOMINAL PAIN NOS	0	0	0	2 (1.3)	1 (0.3)	3 (0.6)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0	0	0	1 (0.7)	1 (0.3)	2 (0.4)
ABDOMINAL WALL INFECTION	0	0	0	1 (0.7)	0	1 (0.2)
ABSCESS NOS	0	0	0	1 (0.7)	0	1 (0.2)
ACUTE CORONARY SYNDROME	0	0	0	0	1 (0.3)	1 (0.2)

atient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment.
Patients are only counted once at each level of summarization.

APPENDIX 10.1

Table ISS SAE 89-4 Serious Adverse Events by Decreasing Frequency in Studies 8 and 9 subjects (continued)

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
ARTHRALGIA	0	0	0	0	1 (0.3)	1 (0.2)
ARTHRITIS INFECTIVE NOS	0	0	0	1 (0.7)	0	1 (0.2)
BREAST CANCER NOS	0	0	0	0	1 (0.3)	1 (0.2)
CEREBROVASCULAR ACCIDENT	0	0	0	0	1 (0.3)	1 (0.2)
CHOLECYSTITIS NOS	0	0	0	0	1 (0.3)	1 (0.2)
DIPLOPIA	0	0	0	0	1 (0.3)	1 (0.2)
GASTROENTERITIS NOS	0	0	0	0	1 (0.3)	1 (0.2)
HYPOGLYCAEMIA NOS	0	0	0	0	1 (0.3)	1 (0.2)
MAJOR DEPRESSIVE DISORDER NOS	0	0	0	0	1 (0.3)	1 (0.2)
OBSESSIVE-COMPULSIVE DISORDER	0	0	0	0	1 (0.3)	1 (0.2)
PANCREATITIS ACUTE	0	0	0	1 (0.7)	0	1 (0.2)
PANCYTOPENIA	0	0	0	0	1 (0.3)	1 (0.2)
PERICARDIAL EFFUSION	0	0	0	0	1 (0.3)	1 (0.2)
PULMONARY OEDEMA NOS	0	0	0	0	1 (0.3)	1 (0.2)
RASH NOS	0	0	0	1 (0.7)	0	1 (0.2)
STAPHYLOCOCCAL INFECTION	0	0	0	1 (0.7)	0	1 (0.2)
STAPHYLOCOCCAL SEPSIS	0	0	0	0	1 (0.3)	1 (0.2)
SYNCOPE	0	0	0	0	1 (0.3)	1 (0.2)
THROMBOCYTOPENIA	0	0	0	0	1 (0.3)	1 (0.2)
URINARY TRACT INFECTION NOS	0	0	0	1 (0.7)	0	1 (0.2)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment.
Patients are only counted once at each level of summarization.

APPENDIX 10.1

Table ISS SAE 89- 5 Serious Adverse Events by Decreasing Frequency in Studies 8 and 9 subjects (continued)

	Dalbavancin 1 dose	Dalbavancin 2 doses	Total Dalbavancin	Comparator 7 days	Comparator 14 days	Total Comparator
AE Preferred Term	**(N=344)**	**(N=594)**	**(N=938)**	**(N=153)**	**(N=316)**	**(N=469)**
VULVAL ABSCESS	0	0	0	0	1 (0.3)	1 (0.2)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. atients are only counted once at each level of summarization.

APPENDIX 10.2

Table ISS SAE 4516- 2 Serious Adverse Events by Decreasing Frequency in Studies 4, 5 and 16 subjects

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
CHOLECYSTITIS ACUTE NOS	0	1 (0.9)	1 (0.5)	0	0	0
CONSTIPATION	0	1 (0.9)	1 (0.5)	0	0	0
DEHYDRATION	0	1 (0.9)	1 (0.5)	0	0	0
DYSKINESIA	0	1 (0.9)	1 (0.5)	0	0	0
GASTRIC VARICES	0	1 (0.9)	1 (0.5)	0	0	0
INTERSTITIAL PNEUMONIA	1 (1.3)	0	1 (0.5)	0	0	0
INTERVERTEBRAL DISC HERNIATION	1 (1.3)	0	1 (0.5)	0	0	0
INTRACRANIAL PRESSURE INCREASED NOS	0	1 (0.9)	1 (0.5)	0	0	0
LUNG ABSCESS NOS	1 (1.3)	0	1 (0.5)	0	0	0
MYOCARDIAL INFARCTION	0	1 (0.9)	1 (0.5)	0	0	0
OSTEOMYELITIS NOS	0	1 (0.9)	1 (0.5)	0	0	0
PANCREATITIS CHRONIC	0	1 (0.9)	1 (0.5)	0	0	0
PLEURAL EFFUSION	1 (1.3)	0	1 (0.5)	0	0	0
PNEUMONIA NOS	1 (1.3)	0	1 (0.5)	0	0	0
POST PROCEDURAL HAEMORRHAGE	1 (1.3)	0	1 (0.5)	0	0	0
POSTOPERATIVE WOUND INFECTION	1 (1.3)	0	1 (0.5)	0	0	0
SICKLE CELL ANAEMIA WITH CRISIS	0	1 (0.9)	1 (0.5)	0	0	0
TOE AMPUTATION	0	1 (0.9)	1 (0.5)	0	0	0

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

APPENDIX 10.2

Table ISS SAE 4516- 3 Serious Adverse Events by Decreasing Frequency in Studies 4, 5 and 16 subjects

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
VOMITING NOS	0	1 (0.9)	1 (0.5)	0	0	0
CEREBROVASCULAR ACCIDENT NOS	0	0	0	0	1 (1.2)	1 (1.0)
FACE OEDEMA	0	0	0	0	1 (1.2)	1 (1.0)
FOOT ULCER	0	0	0	0	1 (1.2)	1 (1.0)
GASTRIC CANCER NOS	0	0	0	1 (4.3)	0	1 (1.0)
GASTROINTESTINAL HAEMORRHAGE NOS	0	0	0	1 (4.3)	0	1 (1.0)
HIP FRACTURE	0	0	0	0	1 (1.2)	1 (1.0)
MENTAL STATUS CHANGES	0	0	0	0	1 (1.2)	1 (1.0)
OSTEOMYELITIS ACUTE NOS	0	0	0	0	1 (1.2)	1 (1.0)
OVERDOSE NOS	0	0	0	1 (4.3)	0	1 (1.0)
PANCREATIC PSEUDOCYST	0	0	0	0	1 (1.2)	1 (1.0)
PHLEBITIS NOS	0	0	0	0	1 (1.2)	1 (1.0)
RENAL FAILURE ACUTE	0	0	0	1 (4.3)	0	1 (1.0)
WOUND INFECTION	0	0	0	1 (4.3)	0	1 (1.0)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

APPENDIX 10.3

Table ISS Tx-Rel SAE 6e: Subjects who Experienced Treatment-Related SAEs in Dalbavancin – Treated subjects (Studies 8 and 9)

Patient's PID	Demography	№ of Doses	SAE	Description	Concomitant Event	Resolution/ Recovery	Action	Assessment
09038020	47 year-old WM	2	Leukopenia	Normal WBC = 4.5 to 10.5 x 10^3 Baseline WBC = 6.9 x 10^3 Day 15, EOT, WBC = 3.7 x 10^3	None	Spontaneous resolution. Day 29 (TOC): WBC = 7.7 x 10^3	None	**Investigator:** Probably related to study drug
09038040	48 year-old WM	2	Leukopenia	Normal WBC = 4.5 to 10.5 x 10^3 Baseline WBC = 9.3 x 10^3, 16.9 % lymphs Nadir (Day 29, TOC) = 2.9 x 10^3, 65.8% lymphs Normal hemoglobin	Viral rhinorrhea	Recovered completely at Day 65	None	Possibly related to study drug

Table ISS Tx-Rel SAE 6f: Subjects who Experienced Treatment-Related SAEs in Comparator (Studies 8 and 9)

Subject PID	Demography	Dose subgroup	SAE	Description	Concomitant Event	Resolution/ Recovery	Action	Sponsor's Assessment
08060007	57 year-old BF	Treated for 8 da	Acute Pancreatitis	Vomiting on Day 4 Dyspnea Day 6, hypertension or Day 8, Delirium: discharged : Dx: alcohol withdrawal Readmitted Day 10: Acute Pancreatitis & erosive gastritis	Alcohol abuse; Other AEs: Rash, Diarrhea, nausea, Vomiting on Day 4 Dyspnea Day 6	Complete recovery by Day 19	New Drug given	Possibly related to study drug
09038038	83 year-old WM	14 days	Thrombocy-topenia	Baseline: Plt=150 x 10^3 ; Day 14 (EOT), Plt = 74 x 10^3 Day 41, Plt= 179 x 10^3	Baseline values of Hb (10.9), HCT (32.3%) low	Complete recovery by Day 41	None	Probably related to drug
09250005	76 year-old WF	15 days	Pancytopenia	Baseline: WBC= 6.0 x 10^3 (nl) Hb (10.9)=low, HCT (32.3%) = low Day 15: WBC= 1.81 x 10 Hb (9.3), HCT(29.2)= further ↓	Abdominal surgical wound infection with *S.aureus* On methotrexate for rheumatica	Complete recovery	Blood, Platelet Leno-grastim given	Possibly related to drug

APPENDIX 10.4

Table ISS Tx-Rel SAE 6g: Subjects who Experienced Treatment-Related SAEs (Studies 4, 5 and 16)

Subject PID	Demography	Dose subgroup	SAE	Description	Concomitant Event	Resolution/ Recovery	Action	Sponsor's Assessment
04009503	63 year-old WF	5 days Vancomycin	Acute renal failure		-	Recovered with sequelae.	Study Drug discont'd	Probably related to drug
16044007	19 year-old HF	13 days Vancomycin	Mild facial edema	Received multiple comparators: Vancomycin, zyvox, moxi-Floxacin.	No further details provided	Complete recovery		Probably related to drug

APPENDIX 10.5

TABLE AE. DISCONT 89. 2 Adverse Events Leading to Discontinuation of Study Medication (studies 8 and 9)

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
CARDIOGENIC SHOCK	1 (0.3)	0	1 (0.1)	0	0	0
CONFUSIONAL STATE	1 (0.3)	0	1 (0.1)	0	0	0
DELUSION NOS	0	1 (0.2)	1 (0.1)	0	0	0
GASTROINTESTINAL DISORDER NOS	1 (0.3)	0	1 (0.1)	0	0	0
HEADACHE	1 (0.3)	0	1 (0.1)	0	0	0
HYPERAESTHESIA	1 (0.3)	0	1 (0.1)	0	0	0
INJECTION SITE PAIN	1 (0.3)	0	1 (0.1)	0	0	0
LEUKOCYTOSIS	0	1 (0.2)	1 (0.1)	0	0	0
LYMPH NODE PAIN	1 (0.3)	0	1 (0.1)	0	0	0
MUSCLE CRAMP	1 (0.3)	0	1 (0.1)	0	0	0
MUSCLE SPASMS	1 (0.3)	0	1 (0.1)	0	0	0
MUSCULOSKELETAL STIFFNESS	1 (0.3)	0	1 (0.1)	0	0	0
NECROTISING FASCIITIS NOS	1 (0.3)	0	1 (0.1)	0	0	0
PARAESTHESIA	1 (0.3)	0	1 (0.1)	0	0	0
PRURITUS	1 (0.3)	0	1 (0.1)	0	0	0
RENAL FAILURE NOS	1 (0.3)	0	1 (0.1)	0	0	0
RENAL FUNCTION TESTS NOS ABNORMAL	1 (0.3)	0	1 (0.1)	0	0	0
RESTLESSNESS	0	1 (0.2)	1 (0.1)	0	0	0
RIGORS	1 (0.3)	0	1 (0.1)	0	0	0

Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment.
Patients are only counted once
at each level of summarization. Adverse events are presented in decreasing frequency of preferred term for the total dalbavancin arm.

APPENDIX 10.5

TABLE AE. DISCONT. 89. 3 Adverse Events Leading to Discontinuation of Study Medication (studies 8 and 9)

AE Preferred Term	Dalbavancin 1 dose (N=344)	Dalbavancin 2 doses (N=594)	Total Dalbavancin (N=938)	Comparator 7 days (N=153)	Comparator 14 days (N=316)	Total Comparator (N=469)
TENOSYNOVITIS	1 (0.3)	0	1 (0.1)	0	0	0
URTICARIA NOS	1 (0.3)	0	1 (0.1)	0	0	0
WHEEZING	1 (0.3)	0	1 (0.1)	0	0	0
ABDOMINAL DISCOMFORT	0	0	0	0	1 (0.3)	1 (0.2)
CEREBROVASCULAR ACCIDENT	0	0	0	0	1 (0.3)	1 (0.2)
HYPERPYREXIA	0	0	0	1 (0.7)	0	1 (0.2)
MALAISE	0	0	0	0	1 (0.3)	1 (0.2)
RENAL FAILURE ACUTE	0	0	0	0	1 (0.3)	1 (0.2)
VARICELLA	0	0	0	0	1 (0.3)	1 (0.2)
VOMITING NOS	0	0	0	1 (0.7)	0	1 (0.2)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

APPENDIX 10.6

TABLE AE. >2% Patients 4516. 2 Adverse Events Reported in >2% of the Patients (Studies 4, 5 and 16)

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
DYSPEPSIA	2 (2.7)	4 (3.5)	6 (3.2)	0	1 (1.2)	1 (1.0)
INSOMNIA	0	5 (4.4)	5 (2.7)	0	5 (6.2)	5 (4.8)
ORAL CANDIDIASIS	0	5 (4.4)	5 (2.7)	1 (4.3)	2 (2.5)	3 (2.9)
ARTHRALGIA	0	5 (4.4)	5 (2.7)	0	2 (2.5)	2 (1.9)
PRURITUS NOS	2 (2.7)	3 (2.7)	5 (2.7)	0	2 (2.5)	2 (1.9)
DIZZINESS	2 (2.7)	3 (2.7)	5 (2.7)	0	1 (1.2)	1 (1.0)
CARDIAC FAILURE CONGESTIVE	2 (2.7)	3 (2.7)	5 (2.7)	0	0	0
HALLUCINATION NOS	1 (1.3)	4 (3.5)	5 (2.7)	0	0	0
PLEURAL EFFUSION	2 (2.7)	2 (1.8)	4 (2.1)	1 (4.3)	3 (3.7)	4 (3.8)
HEADACHE NOS	0	4 (3.5)	4 (2.1)	1 (4.3)	2 (2.5)	3 (2.9)
OEDEMA PERIPHERAL	1 (1.3)	3 (2.7)	4 (2.1)	0	2 (2.5)	2 (1.9)
CONFUSION	1 (1.3)	3 (2.7)	4 (2.1)	0	1 (1.2)	1 (1.0)
RESPIRATORY FAILURE (EXCL NEONATAL)	0	4 (3.5)	4 (2.1)	0	1 (1.2)	1 (1.0)
CATHETER RELATED COMPLICATION	1 (1.3)	3 (2.7)	4 (2.1)	0	0	0
HYPOMAGNESAEMIA	0	4 (3.5)	4 (2.1)	0	0	0
LETHARGY	0	4 (3.5)	4 (2.1)	0	0	0
LIVER FUNCTION TESTS NOS ABNORMAL	2 (2.7)	2 (1.8)	4 (2.1)	0	0	0
BLOOD LACTATE DEHYDROGENASE INCREASED	1 (1.3)	2 (1.8)	3 (1.6)	0	3 (3.7)	3 (2.9)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

APPENDIX 10.6

TABLE AE. >2% Patients 4516. 3 Adverse Events Reported in >2% of the Patients (Studies 4, 5 and 16)

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
PNEUMONIA NOS	2 (2.7)	1 (0.9)	3 (1.6)	1 (4.3)	2 (2.5)	3 (2.9)
WEAKNESS	0	3 (2.7)	3 (1.6)	0	3 (3.7)	3 (2.9)
WOUND INFECTION NEC	2 (2.7)	1 (0.9)	3 (1.6)	0	3 (3.7)	3 (2.9)
LOOSE STOOLS	1 (1.3)	2 (1.8)	3 (1.6)	0	2 (2.5)	2 (1.9)
ALOPECIA	0	3 (2.7)	3 (1.6)	0	1 (1.2)	1 (1.0)
ATRIAL FIBRILLATION	2 (2.7)	1 (0.9)	3 (1.6)	0	1 (1.2)	1 (1.0)
BODY TEMPERATURE INCREASED	0	3 (2.7)	3 (1.6)	0	1 (1.2)	1 (1.0)
DEHYDRATION	0	3 (2.7)	3 (1.6)	1 (4.3)	0	1 (1.0)
DIZZINESS (EXCL VERTIGO)	0	3 (2.7)	3 (1.6)	0	1 (1.2)	1 (1.0)
HYPOAESTHESIA	0	3 (2.7)	3 (1.6)	0	1 (1.2)	1 (1.0)
VAGINOSIS FUNGAL NOS	0	3 (2.7)	3 (1.6)	0	1 (1.2)	1 (1.0)
AGITATION	0	3 (2.7)	3 (1.6)	0	0	0
DYSURIA	0	3 (2.7)	3 (1.6)	0	0	0
PRURITUS	1 (1.3)	1 (0.9)	2 (1.1)	0	5 (6.2)	5 (4.8)
PRESSURE SORE	1 (1.3)	1 (0.9)	2 (1.1)	0	3 (3.7)	3 (2.9)
URTICARIA NOS	1 (1.3)	1 (0.9)	2 (1.1)	2 (8.7)	1 (1.2)	3 (2.9)
HEADACHE	0	2 (1.8)	2 (1.1)	1 (4.3)	1 (1.2)	2 (1.9)
PAIN NOS	1 (1.3)	1 (0.9)	2 (1.1)	0	2 (2.5)	2 (1.9)
PLATELET COUNT INCREASED	0	2 (1.8)	2 (1.1)	0	2 (2.5)	2 (1.9)
POST PROCEDURAL DRAINAGE	0	2 (1.8)	2 (1.1)	0	2 (2.5)	2 (1.9)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

APPENDIX 10.6

Table AE. >2% Patients 4516. 4 Adverse Events Reported in >2% of the Patients (Studies 4, 5 and 16)

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
SOMNOLENCE	1 (1.3)	1 (0.9)	2 (1.1)	0	2 (2.5)	2 (1.9)
CELLULITIS	2 (2.7)	0	2 (1.1)	0	1 (1.2)	1 (1.0)
RESTLESSNESS	0	2 (1.8)	2 (1.1)	1 (4.3)	0	1 (1.0)
WHITE BLOOD CELLS URINE POSITIVE	0	2 (1.8)	2 (1.1)	1 (4.3)	0	1 (1.0)
FALL	2 (2.7)	0	2 (1.1)	0	0	0
HERPES ZOSTER	2 (2.7)	0	2 (1.1)	0	0	0
POST PROCEDURAL PAIN	2 (2.7)	0	2 (1.1)	0	0	0
WHEEZING	2 (2.7)	0	2 (1.1)	0	0	0
DEEP VENOUS THROMBOSIS NOS	1 (1.3)	0	1 (0.5)	0	3 (3.7)	3 (2.9)
FLUSHING	0	1 (0.9)	1 (0.5)	1 (4.3)	2 (2.5)	3 (2.9)
HYPERKALAEMIA	0	1 (0.9)	1 (0.5)	1 (4.3)	2 (2.5)	3 (2.9)
BACTERAEMIA	0	1 (0.9)	1 (0.5)	0	2 (2.5)	2 (1.9)
DYSPNOEA EXACERBATED	1 (1.3)	0	1 (0.5)	0	2 (2.5)	2 (1.9)
ERYTHEMA	0	1 (0.9)	1 (0.5)	0	2 (2.5)	2 (1.9)
HAEMATURIA	0	1 (0.9)	1 (0.5)	1 (4.3)	1 (1.2)	2 (1.9)
PERIPHERAL SWELLING	0	1 (0.9)	1 (0.5)	0	2 (2.5)	2 (1.9)
PHLEBITIS NOS	1 (1.3)	0	1 (0.5)	0	2 (2.5)	2 (1.9)
RENAL IMPAIRMENT NOS	0	1 (0.9)	1 (0.5)	1 (4.3)	0	1 (1.0)
INFUSION SITE ERYTHEMA	0	0	0	0	5 (6.2)	5 (4.8)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

APPENDIX 10.6

Table AE. >2% Patients 4516. 5 Adverse Events Reported in >2% of the Patients (Studies 4, 5 and 16)

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
FOOT ULCER	0	0	0	0	3 (3.7)	3 (2.9)
INFUSION SITE SWELLING	0	0	0	0	3 (3.7)	3 (2.9)
CATHETER RELATED INFECTION	0	0	0	0	2 (2.5)	2 (1.9)
HIP FRACTURE	0	0	0	0	2 (2.5)	2 (1.9)
HYPOALBUMINAEMIA	0	0	0	0	2 (2.5)	2 (1.9)
INFUSION SITE PAIN	0	0	0	0	2 (2.5)	2 (1.9)
INJECTION SITE IRRITATION	0	0	0	0	2 (2.5)	2 (1.9)
LIVER FUNCTION TEST ABNORMAL	0	0	0	0	2 (2.5)	2 (1.9)
RED MAN SYNDROME	0	0	0	1 (4.3)	1 (1.2)	2 (1.9)
SINUS CONGESTION	0	0	0	0	2 (2.5)	2 (1.9)
SKIN ULCER	0	0	0	0	2 (2.5)	2 (1.9)
ANTIBIOTIC LEVEL NOS ABOVE THERAPEUTIC	0	0	0	1 (4.3)	0	1 (1.0)
EMOTIONAL DISTRESS	0	0	0	1 (4.3)	0	1 (1.0)
GASTRIC CANCER NOS	0	0	0	1 (4.3)	0	1 (1.0)
GASTROINTESTINAL HAEMORRHAGE NOS	0	0	0	1 (4.3)	0	1 (1.0)
INFUSION SITE BRUISING	0	0	0	1 (4.3)	0	1 (1.0)
INFUSION SITE TENDERNESS	0	0	0	1 (4.3)	0	1 (1.0)
INSOMNIA EXACERBATED	0	0	0	1 (4.3)	0	1 (1.0)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

APPENDIX 10.6

Table AE. >2% Patients 4516. 6 Adverse Events Reported in >2% of the Patients (Studies 4, 5 and 16)

AE Preferred Term	Dalbavancin 1 dose (N=75)	Dalbavancin 2 doses (N=113)	Total Dalbavancin (N=188)	Comparator 7 days (N=23)	Comparator 14 days (N=81)	Total Comparator (N=104)
LIMB DISCOMFORT NOS	0	0	0	1 (4.3)	0	1 (1.0)
LYMPHADENOPATHY	0	0	0	1 (4.3)	0	1 (1.0)
OVERDOSE NOS	0	0	0	1 (4.3)	0	1 (1.0)
RENAL FAILURE ACUTE	0	0	0	1 (4.3)	0	1 (1.0)
WOUND INFECTION	0	0	0	1 (4.3)	0	1 (1.0)

Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Patients are only counted once at each level of summarization.

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CLINICAL REVIEW

Application Type	21-883
Submission Number	000
Submission Code	N
Letter Date	12/21/04
Stamp Date	12/21/04
PDUFA Goal Date	9/21/05
Reviewer Name	Janice Pohlman, M.D. Menfo A. Imoisili, M.D.
Review Completion Date	9/21/05
Established Name	Dalbavancin
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Lipoglycopeptide
Applicant	Vicuron Pharmaceuticals, Inc.
Priority Designation	P (with 3 month extension)
Formulation	Solid for injection
Dosing Regimen	1000 mg Day 1, 500 mg Day 8
Indication	Complicated Skin and Skin Structure Infections
Intended Population	Adult (> 18 years of age)

Table of Contents

1 EXECUTIVE SUMMARY

Recommendation on Regulatory Action

- The Applicant has submitted a single adequate and well-controlled study with 854 patients demonstrating that dalbavancin administered intravenously at a dose of 1000 mg on Day 1 followed by a 500 mg dose on Day 8 is noninferior to intravenous/oral linezolid 600 mg q 12 hrs for the treatment of complicated skin and skin structure infections (cSSSI) due to susceptible strains of *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, and *Streptococcus agalactiae*. The efficacy findings for this study are supported by (b) (4)

- Based on the analyses of the safety data from 1267 subjects/patients who received dalbavancin in all clinical studies, dalbavancin has been demonstrated to be safe for its intended use. Of the subjects/patients who received dalbavancin, 707 received 2 doses in the Phase 2/3 studies. Nausea, diarrhea and vomiting were the most common clinical adverse events (AEs) and were similar in frequencies across study arms. Cellulitis was the most common serious adverse event (SAE). The frequencies of SAEs were also similar across study arms.

  Clinically significant abnormalities in tabulated laboratory values were identified. The frequencies of ALT/AST elevations <20 x ULN were similar across study arms. Post baseline ALT elevations >20 x ULN occurred in a dalbavancin-treated Phase 3 patient and in a Phase 1 subject who also received dalbavancin. The AST elevations for these two patients were at >10 x ULN– 20 x ULN and >20 x ULN respectively. No patients in the comparator arms had AST/ALT elevation >20 x ULN. Alterations in glucose levels were noted with higher frequencies in dalbavancin-treated patients. In Studies 8 and 9, hypoglycemia (glucose levels ≤0.6 x LLN and ≥0.4-fold decrease) occurred in 5/938 (0.5%) dalbavancin-treated patients compared to none in comparator-treated patients. One of these patients had diabetes mellitus. In all five patients the measured glucose level was <40 mg/dL. All were reported to be asymptomatic. Two patients in Phase 1 who received dalbavancin also developed hypoglycemia. Also in Studies 8 and 9, hyperglycemia (glucose level ≥3x ULN and ≥3-fold increase) was reported in 6 (0.6%) dalbavancin-treated patients versus 1 (0.2%) comparator-treated patient. Four of the 6 dalbavancin-treated cases were diabetic. Three other cases of hyperglycemia were also reported, one each in Study 11 (Phase 1), Study 5 (Phase 2), and Study 16 (Phase 3).

- Dalbavancin has a uniquely long half-life of 9-12 days which may have some clinical safety implications yet unknown. Dalbavancin administered to animals on a daily basis

for extended periods of time resulted in deposition of the drug in body organs and tissues (including the liver, kidneys, and aorta, each of which had dalbavancin levels higher than plasma levels). There is no clinical experience with protracted or repeated courses of dalbavancin and as such, no safety data are available on extended use of dalbavancin.

- These issues not withstanding, the risks associated with the use of dalbavancin for the treatment of cSSSI appear justified by the efficacy demonstrated against potentially life-threatening SSSI, including those due to MRSA. Since the total number of patients exposed to dalbavancin is on the order of 1,000+ patients, the frequency and severity of uncommon AEs will not be clearly defined until actual use in clinical practice along with post-marketing studies occur.

- Sufficient data have been presented to support that the proposed dose of dalbavancin at 1000 mg IV on Day 1, followed by 500 mg IV on Day 8, in the treatment of cSSSI, is a safe and effective dose. In addition, data are available to provide adequate directions for use, and to allow, as needed, dose adjustment (e.g. in patients with severe renal impairment).

Recommendation on Postmarketing Actions

1.1.1 Risk Management Activity

Postmarketing risk management activity must include postmarketing reporting of adverse drug experiences as outlined in 21 CFR 314.80. Prescribing clinicians should be informed through product labeling of the abnormalities in liver function tests and abnormal glucose levels noted in dalbavancin-treated patients relative to comparator-treated patients in clinical trials. Consideration should be given to monitoring for *in vitro* resistance of clinical microbiology laboratory isolates to dalbavancin.

1.1.2 Required Phase 4 Commitments

There are no required Phase 4 commitments related to clinical issues.

1.1.3 Other Phase 4 Requests

Based on abnormal glucose levels (both low and high) observed in dalbavancin-treated patients during clinical trials, a study designed to explore the effect of dalbavancin administration on glucose homeostasis and relationship of glucose levels to dalbavancin pharmacokinetic parameters is recommended. Assessment in both diabetic and non-diabetic patients is recommended and could be performed in conjunction with a dalbavancin efficacy trial in treatment of infected ulcers and other deep (non-cellulitis) soft tissue infections.

Summary of Clinical Findings

1.1.4 Brief Overview of Clinical Program

Dalbavancin (b) (4) is a lipoglycopeptide antibiotic. It is produced as a fermentation product of *Nonomuraea sp*. Dalbavancin has activity against Gram positive aerobic and anaerobic bacteria. The drug interferes with bacterial cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the cell wall peptidoglycan and prevents peptidoglycan crosslinking. The drug product is a sterile, lyophilized solid that is reconstituted with 5% Dextrose for Infusion and administered intravenously. The pharmacokinetic profile of dalbavancin allows for once weekly administration.

The proposed indication for dalbavancin is for treatment of adults with cSSSI caused by Gram positive bacteria including *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, and *Streptococcus agalactiae*. Dalbavancin has also been studied in a Phase 3 clinical trial for treatment of adults with uSSSI caused by Gram positive bacteria and in an exploratory Phase 2 clinical trial in treatment of adults with catheter-related bloodstream infections (CR-BSI) caused by Gram positive bacteria.

A Phase 3 trial, Study VER001-9, was conducted in adult patients with cSSSI. This study treated 854 patients randomized in a 2:1 fashion to dalbavancin or active comparator regimen (linezolid). Another Phase 3 trial, Study VER001-8, was conducted in adult patients with uSSSI and serves as a primary supportive efficacy study for use of dalbavancin in the treatment of cSSSI. This study treated 553 patients randomized in a 2:1 fashion to dalbavancin or active comparator (cefazolin). (b) (4)

The safety database consists of 1267 unique subjects/patients who received dalbavancin. The Phase 1 safety database included 144 exposures (141 patients); 71 healthy subjects received doses ranging from 70 mg to 1600 mg and 73 special population subjects (renal and hepatic impairment) received doses ranging from 70 mg to 1500 mg. The Phase 2/3 safety database included 1126 patients with SSSI or CR-BSI receiving doses ranging from 780 mg to 1500 mg.

There are no sources of clinical data other than studies submitted with this NDA since dalbavancin is not commercially available in any country at this time.

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(b) (4)

1.1.6 Safety

Size of Safety Database

Data from 1267 adults given dalbavancin constitute the safety database. Of these, 1126 patients received dalbavancin in the Phase 2/3 studies; 419 (37.2%) received a single dose and 707 (62.8%) received two doses.

Patients received dalbavancin treatment for the following indications (see table 3):

- cSSSI - studies 9 (571 patients), 5 (41 patients), and 16 (30 patients)
- uSSSI - studies 8 (367 patients) and 16 (77 patients)
- CR-BSI - study 4 (40 patients)

In Phase 1 studies, 141 subjects received dalbavancin. Of these, 29 subjects received 500 mg, 78 received 500-1000 mg, and 34 received > 1000 mg. Seventy three special population subjects (with renal or hepatic impairment) received dalbavancin doses that ranged from 70 mg to 1500 mg.

Table 3: Exposure to study drug in Phases 2 and 3 Studies (by Disease Indication)

		cSSSI				uSSSI				CRBSI			
		D		C		D		C		D		C	
P	S	1 dose	2 doses	7 days	14 days	1 dose	2 doses	7 days	14 days	1 dose	2 doses	7 days	14 days
2	4	0	0	0	0	0	0	0	0	6	34	6	28
	5	21	20	4	17	0	0	0	0	0	0	0	0
3	8	0	0	0	0	273	94	134	52	0	0	0	0
	9	71	500	19	264	0	0	0	0	0	0	0	0
	16	4	26	2	16	45	32	11	20	0	0	0	0
Subtotal		96	546	25	297	318	126	145	72	5	35	6	28
Total		642		322		444		217		40		34	

cSSSI = complicated skin and skin structure; **uSSSI** = uncomplicated skin and skin structure
CRBSI= Catheter-related blood stream infection; **D** = Dalbavancin; **C**= Comparator; **P** = Phase; **S** = Study

The sponsor has therefore provided an acceptable safety database, enough to allow assessment of various categories of adverse events [deaths, other serious adverse events (SAEs), and common adverse events (AEs)]. Rare AEs are not necessarily detectable in a relatively small database (1000 patients).

Duration of Exposure

The dose of dalbavancin studied and proposed for marketing for cSSSI is 1000 mg IV on Day 1, followed by 500 mg on Day 8. Of the 1126 patients who received dalbavancin in the Phase 2/3 database, 707 (62.8%) received this regimen. The receipt of one dalbavancin dose (1000 mg only) was defined as receiving 7 days of treatment. Similarly, receiving two dalbavancin doses (1000 mg on Day 1 and 500 mg on Day 8) was defined as receiving 14 days of treatment. There is no clinical experience to date with exposure to greater than the two dose regimen studied in Phase 3 and no data on repeated courses of dalbavancin.

Common Adverse Events

Overall, 458 (49%) dalbavancin-treated patients reported at least 1 AE, similar to 243 (51.8%) comparator-treated patients. In all the Phase 3 studies, the most common toxicities among dalbavancin-treated patients were related to the gastrointestinal tract: nausea, diarrhea, vomiting and constipation. In all Phase 3 studies combined, dalbavancin-treated patients had nausea at a slightly lower rate than comparator-treated patients (5.4% vs 7.9%). Dalbavancin-treated patients had diarrhea at a similar rate as comparator-treated patients (4.6% vs 5.6%) as did the patients who had vomiting (3.1% vs 3.5%) or constipation (3.1% vs 3.5%). The mean duration of these AEs was 3 days. The frequency of AEs was generally higher in patients who received two doses of dalbavancin or 14 days of comparator treatment compared to patients who received one dose of dalbavancin or 7 days of comparator treatment respectively.

The most common AE outside of the GI tract was headache, occurring in 5.2% of dalbavancin-treated patients versus 6.4% of comparator-treated patients.

Treatment-Emergent Adverse Events (TEAEs)

Although most of the reported AEs were characterized as "unrelated" or "unlikely related" to study drugs, the most common treatment-emergent AEs (TEAEs) in the integrated Phase 2/3 database were also GI tract-related. TEAEs in dalbavancin-treated and comparator-treated patients included diarrhea (3.0% vs 3.7%) and nausea (2.8% vs 3.5%). Others occurring in < 2% of patients included rash (1.4% vs 1%), headache (1.2% vs 1.4%), and vomiting (1.2% vs 1%).

TEAEs Resulting in Discontinuation of Study Drug in Phase 2/3 Studies

Overall, 14/1126 (1.2%) and 12/573 (2.1%) patients developed at least one TEAE resulting in discontinuation of dalbavancin and comparator treatments, respectively. The most common of these AEs was unspecified rash, occurring in 4/1126 (0.4%) dalbavancin-treated and in 2/573 (0.2%) comparator-treated patients. Generalized rash (different from unspecified rash) also occurred in 2/1126 (0.2%) patients leading to dalbavancin discontinuation, whereas none occurred in comparator-treated patients. Other AEs leading to discontinuation of dalbavancin versus the comparator drug included nausea (0.1% vs 0.7%) and unspecified urticaria (0.1% vs 0.3%).

TEAEs Associated with Dropouts from the Studies

Overall dropouts from the studies occurred in 17/1126 (1.5%) dalbavancin-treated patients compared to 6/573 (1.1%) comparator-treated patients. The most common AE resulting in discontinuation of patients from any study was osteomyelitis (unspecified) and occurred in 0.3% and 0.2% of dalbavancin-treated and comparator-treated patients, respectively. Urticaria caused discontinuation from study in 0.1% of dalbavancin-treated and in 0.2% of comparator-treated patients. Other AEs occurred in 0.1% of dalbavancin-treated but none in comparator-treated patients. Cellulitis, anxiety, muscle cramps and musculoskeletal stiffness were some of the other AEs in this category.

Serious Adverse Events (SAEs)

Deaths
Deaths occurred in four studies (three SSSI studies and one CR-BSI study, as shown in table 4 below). Thus, 9/ 1126 (0.8%) Phase 2/3 patients who received dalbavancin died. By comparison, 7/573 (1.2%) patients who received the comparator treatment in the Phase 2/3 studies died. All patients had serious co-morbid conditions and were receiving many concomitant medications. Of the nine deaths in the dalbavancin arm, 6/9 (66.7%) occurred among patients who received a single dose, and 3/9 (33.3%) in patients who received two doses. There was no patient in whom the direct contribution of dalbavancin to the patient's death was apparent.

Table 4: Number of Reported Deaths

study number	Number of Deaths					
	Study Drug	**# of Pts (N)**	**Deaths n (%)**	**Comparator**	**# of Pts (N)**	**Deaths n (%)**
Study 4	Dalbavancin	40	3 (7.5)	Vancomycin	34	2 (5.9)
Study 8	Dalbavancin	367	3 (0.82)	Cefazolin	186	3 (1.6)
Study 9	Dalbavancin	571	2 (0.35)	Linezolid	283	2 (0.7)
Study 16	Dalbavancin	107	1 (0.93)	Vancomycin	156	0
Total	**Dalbavancin**	**1085**	**9 (0.83)**	**Comparator**	**659**	**7 (1.1)**

Other Serious Adverse Events

Overall, 92/1126 (8.2%) dalbavancin-treated patients and 54/573 (9.4%) comparator-treated patients had at least one SAE in the Phase 2/3 studies. Cellulitis, reported by 13 (1.2%) dalbavancin-treated patients and 5 (0.9%) comparator-treated patients was the most frequent SAE. The frequency of cellulitis was numerically similar between patients who received one dose of dalbavancin vs 7 days of comparator treatment (1.4% vs 1.7%) and those who received two doses vs 14 days treatment (1.0% vs 0.5%). Other SAEs, including congestive heart failure, accidental overdose, atrial fibrillation, leukopenia, and others, occurred with a frequency of ≤1% in any treatment arm.

Treatment-Emergent SAEs (TESAEs)

Two patients (0.2%) treated with dalbavancin and 5/573 (0.9%) patients treated with a comparator drug, developed SAEs that were considered treatment- related. The two dalbavancin-treated patients developed leukopenia on treatment (tables 6 and 7) and were considered to be possible dalbavancin treatment- related SAEs. There were no treatment-related SAEs of leukopenia among the comparator-treated patients. Other SAEs reported only in the comparator arm of the studies are shown in table 5.

Table 5: Treatment-Related SAEs in Phase 2/3 Studies

Preferred Term	**Dalbavancin**			**Comparator**		
Number (%) of Patients	**1 Dose (n=419)**	**2 Doses (n=707)**	**Total (n= 1126)**	**7 Days (n= 176)**	**14 days (n= 397)**	**Total (n= 573)**
Leukopenia NOS	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Pancreatitis acute	0	0	**0**	1 (0.6)	0	**1 (0.2)**
Pancytopenia	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Thrombocytopenia	0	0	**0**	0	1 (0.3)	**1 (0.2)**
Renal failure	0	0	**0**	1(0.6)	0	**1 (0.2)**
Face Edema	0	0	**0**	0	1(0.3)	**1(0.2)**

Treatment-related SAEs were defined as those reported as possibly or probably related to study treatment or AEs whose relationship was missing. Patients are counted only once at each level of summarization.

Table 6: WBC Transition Profile:Treatment-Related Leukopenia (First Patient)

	Baseline	Day 9	Day 15 EOT)	Day 29 TOC)	Comments
WBC	6.9 $10^3/\mu$	4.0 $10^3/\mu$	3.7 $10^3/\mu$	7.7 $10^3/\mu$	No concurrent illness Leukopenia probably related to Rx. Patient recovered by Day 29. No further action taken.
Diff	63.4 S 16.1 M 17.1 L	45 S 12.2 M 4.2 E	39.8 S 38.8 L 13.6 M 5.3 E 2.5 B	47.2 S 11.1 M 37.6 L 2.7 E	
WBC Normal range = 4.5 – 10.5 x $10^3/\mu$ S=segmented neutrophil, L=lymphocyte, M=monocyte, E=eosinophil, B=basophil					

Table 7: WBC Transition Profile:Treatment-Related Leukopenia (Second Patient)

	Baseline	Day 8	Day 15 (EOT)	Day 29 (TOC)	Inv. Assessment
WBC	9.3x $10^3/\mu$	7.0x $10^3/\mu$	6.9 x $10^3/\mu$	2.6x $10^3/\mu$	Patient had a viral URI unlikely related Total recovery (D 65) No action taken
Diff. (%)	72.5 S 16.9 L 9.7 M 0.5 E plt 200	65.8 S 22.8 L 2.6 E plt 382	56.7 S 34.0 L 1.9 E	24.3 S 65.8 L 6.5 M 2.6 E	
WBC Normal range = 4.5 – 10.5 x $10^3/\mu$ S=segmented neutrophil, L=lymphocyte, M=monocyte, E=eosinophil, B=basophil, plt=platelet					

Laboratory Abnormalities of Significance

Hepatobiliary

In preclinical studies, rats and dogs who received dalbavancin developed hepatocellular necrosis, vacuolization and degeneration after 3 months treatment. In clinical Studies 8 and 9, the overall ALT elevations at various levels above the ULN are shown in table 8.

ALT elevations of <20 x ULN were comparable across study arms or slightly less frequent in dalbavancin-treated patients than in comparator-treated patients. However, outlier elevations of >20 x ULN were found only in patients who received dalbavancin; two patients in Study 8 and one Phase 1 subject had ALT >20 x ULN.

- One of the two patients in Study 8 reported a history of Tylenol abuse and had an ALT value of 1402 U/L at baseline.
- The second patient in Study 8 had inadequate clinical evaluation to explain his liver enzyme elevation except that he drank excessive amounts of alcohol during the study period. The degree of elevation and the ALT/AST ratio was against the diagnosis of acute alcoholic hepatitis. Dalbavancin-related hepatocellular injury could not be excluded in this case.
- The liver enzyme elevation in the Phase 1 subject was confounded by a new diagnosis of acute hepatitis C, although rapidity of ALT elevation and the level to which it rose was generally uncharacteristic of hepatitis C.

The latter two cases above with ALT elevation occurring after treatment with dalbavancin was initiated are confounded and the data collected to evaluate the nature of the hepatic injury were not complete. Therefore, causal association with dalbavancin administration can not be

excluded. In a database of 1000+ patients, uncommon TEAEs may not arise. Prescribing clinicians should be informed through product labeling of the abnormalities in liver function tests noted in dalbavancin-treated patients in clinical trials.

Bilirubin elevations (>1.5 x ULN) and alkaline phosphatase abnormalities (>1.5 x ULN) occurred with frequencies that were similar across treatment arms. No case met Hy's Law.

Table 8: Overall Alanine Aminotransferase (ALT) and Bilirubin Abnormalities for Studies 8 and 9

	Dalbavancin N = 938			**Comparator N = 469**		
By ALT	**1 dose n (%) =344**	**2 doses n (%) =594**	**Total N (%) =938**	**7 days n (%) =153**	**14days n(%) =316**	**Total N(%) =469**
>20xULN	1 (0.3)	1 (0.2)	**2 (0.2)**	0	0	**0**
>10xULN - 20xULN	0	0	**0**	0	0	**0**
>5x-10xULN	3 (0.9)	2 (0.4)	**5 (0.5)**	0	5 (1.5)	**5 (1.1)**
>3x-5xULN	5 (1.4)	14 (2.4)	**19 (2.0)**	0	11 (3.5)	**11(2.3)**
By Bili >1.5 x ULN						
↑ from normal baseline levels	2 (0.6)	3(0.5)	**5 (0.5)**	1(0.7)	1 (0.3)	**2 (0.4)**
↑ from abnormal baseline levels	6 (1.7)	17 (2.9)	**23 (2.5)**	4 (2.6)	6 (1.9)	**10 (2.1)**
Total	8 (2.3)	20 (3.4)	**28 (3.0)**	5 (3.3)	7 (2.2)	**12 (2.5)**
ULN = Upper Limit of Normal; **ALT=** Alanine Aminotransferase. There were no cases that satisfied Hy's Law						

Glucose Metabolism

In preclinical studies in rats and dogs, vacuolization and degeneration of the acinar cells of the pancreas were reported. It is uncertain whether these dalbavancin-associated events can also occur in humans and, if so, whether the pathology extends to the islets cells, with a potential for adverse impact on glucose metabolism. It is also possible that the human pancreas is unaffected. Amylase and lipase values were not provided by the sponsor.

Table 9 shows patients that had increases in glucose levels (≥3 x ULN and ≥3-fold increase) while receiving dalbavancin or the comparator in Studies 8 and 9. As shown in the table, 6/938 (0.6%) dalbavancin-treated patients had such increases in blood glucose levels compared to 1/469 (0.2%) patient who was comparator-treated. Four of the six dalbavancin-treated cases were, however, confounded by diabetes mellitus.

Table 9: Hyperglycemia in Studies 8 and 9 Patients (Glucose Transition Profiles)

PTID	Dalbavancin Arm	Baseline	Day 8	EOT	TOC	(+) DM	Comments
08071003	1dose	161	-	487	498	**Yes**	
08009011	2 doses	125	462	165	176	**Yes**	
09009023	2 doses	135	455	99	126	No	No SP comments
09023006	2 doses	108	-	375	395	**Yes**	
09050007	2 doses	132	425	111	124	No	AE= Hyper
09037021	2 doses	358	-	1146	-	Yes	
PTID	**Comparator Arm**	**Baseline**	**Day 8**	**EOT**	**TOC**	**(+) DM**	
-	Comparator 7 days	-	-	-	-		
09005065	Comparator 14 days	98	347	98	-	No	
DM = Diabetes Mellitus; Hyper = Hyperglycemia; SP= Sponsor - = value not provided ; value provided incompatible with hyperglycemia							

In Table 10, five (0.5%) dalbavancin-treated patients had decreases in serum glucose (glucose levels ≤0.6 x LLN and ≥0.4-fold decrease) compared to none in the comparator arm of the studies. One patient had diabetes mellitus. In all five patients the measured glucose level was <40 mg/dL. All patients were reported to be asymptomatic.

Table 10: Hypoglycemia in Studies 8 and 9 Patients (Glucose Transition Profiles)

PTID	**Dalbavancin Arm**	**Baseline**	**Day 8**	**EOT**	**TOC**	**(+) DM**	**Comments**
08029003	1dose	70	-	30	86	No	-
09001007	2 doses	87	132	36	114	No	AE= HG
09017006	2 doses	98	38	92	62	No	
09081002	2 doses	100	50	31	70	No	AE = a-HG
09250002	2 doses	115 (6.4)	18	39.5(2.2)	6.5	**Yes**	
PTID	**Comparator Arm**	**Baseline**	**Day 8**	**EOT**	**TOC**	**(+) Diabetes**	
-	7 days	-	-	-	-	-	
-	14 days	-	-	-	-	-	
AE= Adverse event; DM = Diabetes Mellitus; a-HG = asymptomatic Hypoglycemia; HG = Hypoglycemia;							

Despite the small number of these cases, and because of the limited size of the safety database, the safety profile in these populations may not have been fully characterized with respect to glucose metabolism in individuals who received dalbavancin treatment in these studies. Post-marketing surveillance may provide additional information.

1.1.7 Dosing Regimen and Administration

The dosing regimen of dalbavancin studied in the treatment of cSSSI is 1000 mg administered intravenously on Day 1, followed by a second dose of 500 mg administered intravenously on Day 8.

1.1.8 Drug-Drug Interactions

Dalbavancin is not a substrate, inhibitor, or inducer of enzymes in the cytochrome P450 system. In clinical studies, dalbavancin pharmacokinetics were not affected by cytochrome P450 substrates, inducers, or inhibitors, or individual medications including acetaminophen, aztreonam, fentanyl, metronidazole, furosemide, proton pump inhibitors, midazolam, and simvastatin.

1.1.9 Special Populations

Based on Phase 1 studies in 28 subjects with varying degrees of renal insufficiency, no dosage adjustment is necessary in patients with $CL_{CR} \geq 30$mL/min. The dose of dalbavancin recommended by the biopharmaceutical reviewer in patients with severe renal impairment (CL_{CR} <30mL/min) is 750 mg on Day 1 and 375 mg on Day 8. No dosage adjustment is necessary for patients receiving regularly scheduled hemodialysis.

Based on a Phase 1 study in 17 subjects with mild, moderate, or severe hepatic impairment, no dosage adjustment is recommended for patients with mild hepatic insufficiency. However, subjects with moderate to severe hepatic insufficiency had lower concentrations of dalbavancin as measured by mean area under the curve ($AUC_{0\text{-}336\ hr}$). The clinical significance of this finding in patients is not known.

Dalbavancin has not been studied in the pediatric population.

2 INTRODUCTION AND BACKGROUND

Product Information
Description: Dalbavancin is a semisynthetic lipoglycopeptide antibiotic produced by chemical modification of a natural glycopeptide produced by *Nonomuraea* sp.
Generic Name: Dalbavancin
Proposed Trade Name: (b) (4)
Chemical Class: New molecular entity (NME)
Pharmacological class: Lipoglycopeptide (structural similarity to vancomycin and teicoplanin)
Proposed indication, age group, dosing regimen: Complicated skin and skin structure infections in adults dosed as a single 1000 mg IV dose on Day 1, followed by a 500 mg IV dose on Day 8.

Currently Available Treatment for Indications
The following treatments are FDA approved and available for the treatment of cSSSI, including those caused by Gram positive pathogens:

- Daptomycin
- Ertapenem
- Levofloxacin
- Linezolid
- Meropenem
- Piperacillin/tazobactam
- Quinupristin/dalfopristin
- Tigecycline

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

- Daptomycin
- Linezolid
- Tigecycline

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

Availability of Proposed Active Ingredient in the United States
This product is a NME and is not currently marketed in the United States.

Important Issues With Pharmacologically Related Products
This product has been described by the Applicant as being structurally related to teicoplanin, a glycopeptide antimicrobial (b) (4) Dalbavancin has also been compared to the glycopeptide, vancomycin, by the Applicant during the course of development. Vancomycin is available for treatment of serious or severe infections due to Gram positive organisms in the US and outside the US, while teicoplanin is only available outside the U.S.

Issues associated with vancomycin: One of the most commonly cited adverse events associated with infusion of vancomycin is "red man syndrome" characterized by erythema, pruritus, and flushing and occasionally accompanied by hypotension. The actual incidence of "red man syndrome" is uncertain, and appears to be related to the rate of infusion, particularly with the first dose. Additional adverse events include hypersensitivity reactions (fever, rash, and pruritus), nephrotoxicity (more commonly associated with earlier, less purified preparations) including interstitial nephritis, and anecdotal reports of reversible neutropenia and thrombocytopenia. Reports of otoxicity in humans are often confounded by concomitant administration of aminoglycosides and ototoxicity has not been demonstrated in animal studies.

(b) (4)

(b) (4)

Presubmission Regulatory Activity

June 22, 2000, Pre-IND Meeting: The primary objectives of the meeting were to discuss the results of a Phase 1 study completed in the United Kingdom and get Agency comments on the proposed study design for the first clinical trial in the United States. The UK Phase 1 study had incorporated audiologic testing based on information contained in the Adverse Reactions section of the vancomycin label. The Applicant, based on a blinded review of audiometry findings in this study by two expert audiologists, attributed the abnormal findings in five subjects receiving VER001 (dalbavancin) and two subjects receiving placebo, to random variability and inadequately controlled audiometry testing conditions. The Agency recommended that the Applicant (Versicor) conduct high frequency audiometry testing to include frequencies up to 12 kHz with concomitant otoacoustic emission testing in the proposed US Phase 1 protocol. The Agency also recommended that the Applicant conduct an additional animal study (either in the guinea pig or dog) to screen for potential ototoxicity.

1 Wilson, APR. Comparative Safety of Teicoplanin and Vancomycin. International Journal of Antimicrobial Agents 10 (1998): 143-152.

July 13, 2000, IND 60,613 was submitted to the Agency: The proposed study was a Phase 1 study of safety, pharmacokinetics, and dose-limiting toxicity of VER001 (dalbavancin) in healthy subjects. The Agency requested high frequency audiometry testing with frequencies up to 16 kHz and recommended investigation of the vestibular effects of VER001 (dalbavancin).

August 10, 2000, IND Teleconference: FDA requested that Versicor consider a lower starting dose ((b) (4) for the single dose portion of the Phase 1 study. Versicor also agreed to incorporate audiometric testing with frequency ranges up to 16 kHz and to incorporate a self-assessment questionnaire to address vestibular testing in this study.

October 25, 2001, Clinical Development Meeting: The primary objectives of the meeting were to reach agreement on the design of Phase 2 studies and to reach agreement on the need for continued audiology testing in Phase 2 studies. The Applicant presented results from the US Phase 1 study in healthy adult subjects, along with an expert audiologist's opinion report (b) (4) that concluded that dalbavancin was not ototoxic based on negative audiometry findings in 38 subjects in the Phase 1 study. The Agency expressed concern with the conclusion that dalbavancin was not ototoxic based on data in 38 subjects and recommended that the Applicant (Versicor) continue high frequency audiometry in the Phase 2 SSSI study (VER001-5). (b) (4)

November 21, 2001, FDA Comments transmitted by facsimile to Versicor: Comments pertained to the proposed Phase 1 studies in subjects with renal impairment, VER001-3 and VER001-6, and the Phase 2 SSSI study, VER001-5. The Division also acknowledged the lack of evidence of ototoxicity in 38 subjects treated with dalbavancin in the US Phase 1 study. The Division recommended that high frequency audiometry testing (up to 16 kHz) be continued in specific subgroups such as subjects with potential for altered metabolism of the drug (i.e., renal impairment subjects in Phase 1), the elderly, and patients receiving concomitant medications raising the risk for ototoxicity.

December 6, 2001, Teleconference Follow-up to October Clinical Development Meeting: The majority of the teleconference focused on the proposed Phase 2 study of dalbavancin in the treatment of CR-BSI (VER001-4). Areas of Agency concern included: (b) (4) The Agency planned to provide the Applicant with additional written comments on the CR-BSI protocol.

February 27, 2002, Teleconference Follow-Up to October FDA Comments for VER001-4: The Applicant expressed concern about the Agency's recommendation to exclude patients with mild renal impairment from this study. The Applicant agreed to conduct a covariate analysis characterizing whether body weight is a significant factor affecting plasma dalbavancin concentrations in patients with impaired renal function. The Applicant also proposed (b) (4)

October 30, 2002, End-of-Phase 2 Meeting: The meeting objectives were to discuss the clinical development program for dalbavancin. The following agreements were reached:

- A safety database of 1200 patients, absent a safety signal, should be sufficient for a NDA package.
- One adequate and well-controlled trial in uSSSI (VER001-8), one adequate and well-controlled trial in cSSSI (VER001-9), and one supportive non-US study in cSSSI (b) (4)
- Based on information provided in the briefing package, the proposed regimen of a 1000 mg loading dose, followed by a 500 mg dose one week later seems appropriate. However, FDA recommended that Versicor collect additional PK/PD information to support the chosen dose.
- The Applicant's choices of comparator (cefazolin/cephalexin for VER001-8 and linezolid for VER001-9) were acceptable.
- The Applicant's criteria for distinguishing between cSSSI and uSSSI were acceptable.
- Audiologic assessments could be discontinued in clinical trials.
- The Applicant's proposal to screen for drug interactions with population pharmacokinetic (PK) analyses was acceptable. FDA recommended that the Applicant conduct *in vitro* metabolism studies using human microsome preparations to determine if dalbavancin was a substrate or inhibitor and/or inducer for cytochrome P450 enzymes.

Agency requests included:

- The Applicant should study dalbavancin's potential for cardiac effects with *in vitro* hERG and Purkinje fiber studies and an *in vivo* conscious dog telemetry study.
- The Applicant should characterize the metabolite profile.
- The Applicant should select a delta (non-inferiority margin) that would be sufficient to demonstrate robust results; a larger sample size (with a smaller delta) would provide a stronger NDA package.
- The Applicant should collect additional PK/PD information to support the chosen dose.
- The Applicant should propose susceptibility breakpoints prior to Phase 3.
- Although the Pediatric Rule was not in effect, pediatric drug development was encouraged.

Unresolved issues at the end of the meeting included:

- Timing of the test-of-cure visit and follow-up assessments.

January 23, 2003, Teleconference Follow-Up to EOP2 Meeting: The purpose was to clarify comments received from FDA and to continue discussion on the timing of test-of-cure visit for the Phase 3 SSSI protocols. FDA reinforced that in non-inferiority testing, the Per Protocol

(clinically evaluable) and Intent To Treat (ITT) efficacy analyses serve as co-primary analysis populations for the trial. Versicor proposed a late follow-up telephone interview approximately 2 weeks after the TOC visit to capture late failures as a means of satisfying FDA's request to have a follow-up based on day of enrollment rather than the last day of therapy. Versicor planned to amend Study VER001-8.

(b) (4)

September 25, 2003, FDA Comments transmitted by facsimile to Versicor: The Agency acknowledged the lack of evidence of ototoxicity from stringent audiometry testing in at least 45 healthy human subjects. Based on these results (and therefore any confirmation of the random ototoxicity findings of the original UK Phase 1 study), the Agency agreed with discontinuation of strict audiologic monitoring in further clinical studies of dalbavancin. Close medical monitoring for AEs related to hearing and balance were recommended and if detected, the Agency reserved the right to revisit the issue of audiologic monitoring with the Applicant.

(b) (4)

November 7, 2003, Fast Track Designation for cSSSI: Fast Track designation was granted for the development of dalbavancin for the treatment of cSSSI.

May 11, 2004, Pre-NDA Meeting: This meeting was held to discuss the content and format for the electronic submission of the NDA and the appropriate integration of study populations for safety and efficacy analyses. Also discussed were the use of population pharmacokinetic data to screen for possible drug-drug interactions, the proposed pediatric plan, and the *in vitro* susceptibility breakpoint plan. The Agency recommended that the Applicant conduct a juvenile animal study prior to human testing and agreed with the Applicant's plan to submit a deferral request for the pediatric development plan until that study was completed.

September 7, 2004, Teleconference between the Applicant and the Agency CMC review team: The Agency noted that significant changes had been made in dalbavancin since the manufacturing of product for the Phase 3 clinical trials. The Applicant was provided with a list of issues that needed to be addressed and reviewed prior to submission of the NDA.

October 29, 2004, Follow-up Pre-NDA Meeting (Clinical Review Meeting): The primary focus of the meeting was a discussion of the results from the Phase 3 cSSSI study, particularly the difference in the point estimates for the difference in response rates (dalbavancin – linezolid) in the ITT and CE analyses (b) (4)).The Agency suggested that the

Applicant continue to explore the reasons for this difference in additional *post hoc* sensitivity analyses.

February 18, 2005, NDA Filing Letter: The Applicant was notified of the fileability of the NDA, along with notification of Priority Review status with user fee goal date of June 21, 2005.

April 29, 2005, Teleconference to discuss Applicant's pediatric development plan: Agreements reached:

(b) (4)

May 5, 2005, Letter to Applicant: The Applicant was notified about the 3 month extension of the user fee goal date to September 21, 2005, based on receipt of a major CMC amendment received September 4, 2005.

Other Relevant Background Information

(b) (4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Dalbavancin is a semi-synthetic antibiotic manufactured by chemical modification of the glycopeptide antibiotic A-40,926 which is produced by fermentation of *Nonomuraea* sp. It is a mixture of five closely related homologues known as A_0, A_1, B_0, B_1, and B_2, differing primarily in the structure of the fatty acid side chain. Two of the homologues, B_0 and B_1, make up approximately (b) (4) of the drug product. The drug product is manufactured by (b) (4)

The drug product is supplied as a sterile, lyophilized powder in single-dose vials without preservative. The Applicant is proposing (b) (4) 500 mg dose vials for commercial marketing, although stability testing was performed (b) (4) (b) (4) Single dose vials must be reconstituted with Sterile Water for Injection and diluted with 5% Dextrose for Infusion, since saline-based infusions cause precipitation. (b) (4)

A number of issues were identified by the Chemistry Review team regarding the manufacturing process, including characterization of the master cell bank, and analytic methods related to dalbavancin. Please see the Chemistry Review done by Rapti Madurawe, Ph.D. for details regarding the chemistry issues and deficiencies. The Product Quality Microbiology Review done by John Metcalfe, Ph.D., did not identify any product microbiology deficiencies.

3.2 Animal Pharmacology/Toxicology

In both rats and dogs, the primary sites of toxicity were the liver and kidney. Both rats and dogs had elevations of ALT/AST along with alterations in cholesterol, protein, and triglyceride plasma levels. Elevations of AST/ALT in the 3-month dog studies (with animals receiving drug on a daily basis) persisted for greater than 15 months. Histopathologic changes in the liver included hepatocellular necrosis (described as centrolobular in the 3 month dog study), vacuolization, and degeneration. Elevation of BUN was seen in both rats and dogs, with changes of diminishing severity persisting in dogs through the 15 month post-dosing period. Histopathologically, tubular vacuolization, degeneration, and necrosis were noted, with primarily tubular necrosis and glomerulonephritis noted in the 3 month dog study. Histopathologic changes were also noted in the pancreas, with greater frequency in the rat, and consisted of pancreatic vacuolization, degeneration, apoptosis, and acinar atrophy. Dose limiting toxicity in the 1- and 3-month rat studies was related to injection site damage. Evidence of a histaminic response (ear congestion, mucosal pallor) with salivation was noted in dogs at doses of 40-60 mg/kg.

Evaluation of the effect of dalbavancin on cardiac conduction in animals included a hERG assay, Purkinje fiber assay, anesthetized dog study and a conscious, telemetrized dog study. The hERG assay was negative; the maximum level feasible for testing was below plasma levels seen in humans. The Purkinje fiber assay was negative, but the positive control did not show an effect.

Anesthetized dogs did not show a change in blood pressure or ECG tracings at doses up to 20 mg/kg, nor did telemetrized dogs at doses up to 60 mg/kg.

Reproductive toxicity studies were performed in rats and rabbits. No embryotoxic or embryolethal effects were seen in the Segment II study in the rabbit at doses up to 15 mg/kg/day during organogenesis. In the rat, the fetal NOAEL was 15 mg/kg/day with delayed ossification in the sternebrae and skull. In the segment III rat study, increased lethality (stillborn/unexplained early death in first week postpartum) was seen at the high dose (30 mg/kg/day to the dams), with NOAEL of 15 mg/kg/day. No effects on developmental milestones of the F2 generation were observed. Dalbavancin levels in both pups' plasma and mothers' milk were approximately 1/10th of the maternal plasma levels of the compound. Dalbavancin was negative of mutagenicity and clastogenicity in the standard battery of assays.

For more detailed information, please refer to the Pharmacology/Toxiciology Review done by Wendelyn Schmidt, Ph.D.

3.3 Microbiology

Dalbavancin is a lipoglycopeptide antibiotic which interferes with bacterial cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide of the cell wall peptidoglycan and preventing cross-linking. Dalbavancin has activity against Gram positive aerobic and anaerobic organisms. The results of studies designed to detect resistant mutants of staphylococci in the presence of dalbavancin and vancomycin indicate that serial passage of *S. aureus* and *S. epidermidis* did not lead to development of stable resistance. Susceptibility testing for dalbavancin is done by microdilution methods; (b) (4). During evaluation of the microdilution methodology, it was determined that in order to obtain consistent results with fresh or frozen panels, Polysorbate-80 (P-80) must be added to the panels. Addition of P-80 was not required for dry-format panels. The Applicant has proposed susceptibility breakpoints for dalbavancin of (b) (4) MIC ranges for dalbavancin for clinical and surveillance isolates were 0.015 to 0.25µg/mL for SA (including 25 VISA isolates) and <0.015 to 0.12µg/mL for streptococci. Based on data from the clinical trials and the PK/PD analysis, the Agency proposes a susceptibility breakpoint of ≤0.06µg/mL for *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus agalactiae*.

For more detailed information, please refer to the Microbiology Review done by Connie Mahon, M.S.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of data used for this review included the individual clinical study reports (VER001-8 and VER001-9) along with selected case report forms (CRFs) and study datasets, and the Common Technical Document (CTD). Information was supplied in electronic format and was accessed through the Electronic Document Room (EDR) at the following links:

\\CDSESUB1\N21883\N_000\2004-12-21
\\CDSESUB1\N21883\N_000\2005-02-24
\\CDSESUB1\N21883\N_000\2005-04-01
\\CDSESUB1\N21883\N_000\2005-05-18

4.2 Tables of Clinical Studies

A tabular list of all clinical studies with dalbavancin was provided by the Sponsor. Tables listing the studies have been adapted from the Applicant's NDA submission. Table 11 includes the Phase 1 studies designed to collect safety, tolerability and pharmacokinetic data in healthy subjects or special populations of subjects. Table 12 includes the Phase 2 and Phase 3 clinical studies in patients with infection. The majority of the Phase 2/3 studies were performed in patients with skin and skin structure infections (SSSI).

Table 11: Phase 1 Pharmacokinetic and Safety Studies

Study Number	Design	Objective	Study Population	Dose Regimen	Number Treated
VER001-1 (UK)	R, PC Dose escalation Single Center	Safety, PK, and detection of dose-limiting toxicity	Healthy adults, ages 18-60	Single (70, 140, 22, 360 mg) Multiple (70 mg daily for 7 days)	Single 11 Multiple 6 Placebo 6
VER001-2 (US)	R, PC Dose Escalation Single Center	Safety, PK, and detection of dose-limiting toxicity Assess tissue penetration (skin blister)	Healthy adults, ages 18-55	Single (140, 220, 350, 500, 630, 840, 1120 mg) Multiple (Day 1 loading dose, then daily dose x 6 days) 300/30 mg, escalation 400/40, 600/60, 800/80, 1000/100	Single 21 Multiple 18 Placebo 13
VER001-3 (US)	R, PC Single Center	PK in subjects with mild to moderate renal impairment	Adults, age 18-75, mild to moderate renal impairment	Single (70 mg)	Single 3 Placebo 2
VER001-10 (US)	R, OL, Uncontrolled Single Center	Assessment of skin concentration, calculation of extent of renal clearance	Adults, ages 18-65, normal baseline audiology	Single (1000 mg)	6
VER001-11 (US)	R, OL, Uncontrolled Single Center	Safety, PK, and tolerability Subjects with severe renal impairment or ESRD versus age, gender, and weight-matched healthy subjects	Adults, ages 18-80, severe renal impairment, ERSD, or healthy subjects	Single (500 or 1000 mg)	Severe renal impairment 10 ESRD 6 No renal impairment 6

Table 11 (cont): Phase 1 Pharmacokinetic and Safety Studies

Study Number	Design	Objective	Study Population	Dose Regimen	Number Treated
VER001-12 (US)	R, OL, Uncontrolled Single Center	Safety, PK, and tolerability in subjects with hepatic impairment versus age, gender, and weight-matched healthy subjects	Adults, ages 18-80, mild, moderate, or severe hepatic impairment, or healthy subjects	IV dalbavancin 1000 mg on Day 1 and 500 mg on Day 8	Mild hepatic impairment 6 Moderate hepatic impairment 6 Severe hepatic impairment 5 No hepatic impairment 10
VER001-13 (US)	R, OL, Uncontrolled Single Center	Safety, PK, and tolerability in subjects with mild to moderate renal impairment versus age, gender, and weight-matched healthy subjects	Adults, ages 18-80 years, with varying degrees of renal function	Single (1000 mg)	Mild renal impairment 6 Moderate renal impairment 6 No renal impairment 9
VER001-19	OL Uncontrolled Single center	Safety, excretion, and skin blister concentration	Adults, ages 19-65 years	Single (1000 mg)	9
Adapted from NDA 21-883, CTD Module 2.7.6 R=randomized, PC=placebo controlled, OL=open-label, PK=pharmacokinetic, ESRD=end-stage renal disease					

Table 12: Phase 2 and Phase 3 Efficacy and Safety

Study Number	Phase	Indication	Dose of Dalbavancin	Comparator	Number of Patients Randomized
VER001-4	2	Catheter-related Bloodstream Infection (CR-BSI)	1) 650mg, then 65mg daily for 7-14 days 2) 1000mg Day 1 ±500mg Day 8	Vancomycin 1000mg IV q12h x 7-14 days	1) Dalbavancin N=7 2) Dalbavancin N=33 Vancomycin N=34
VER001-5	2	Skin and Skin Structure Infection (SSSI) (mixed: uncomplicated and complicated)	1) 1100mg x 1 2) 1000mg Day1 ±500mg Day 8	Prospectively chosen by the investigator with duration determined by the investigator	1) Dalbavancin N=20 2) Dalbavancin N=21 Comparator N=21
VER001-8	3	uSSSI (warranting parenteral therapy)	1000mg Day 1 ± 500mg Day 8	Cefazolin 500mg IV q8h /cephalexin 500mg PO qid x 7 or 14 days	Dalbavancin N=367 Cefazolin N=186
VER001-9	3	cSSSI	1000mg Day 1 +500mg Day 8	Linezolid IV to PO 600mg q12h x 14 days	Dalbavancin N=571 Linezolid N=283
VER001-16	3	uSSSI and cSSSI (enriched for MRSA)	1000mg Day 1 ±500mg Day 8	Vancomycin 1000mg IV q12h / PO switch based upon *in vitro* data x 7 or 14 days	Dalbavancin N=107 Vanconmycin N=49
Adapted from NDA 21-883, CTD Module 2.5 Clinical Overview, Table 1 (page 14)					

4.3 Review Strategy

The clinical review of this NDA was divided into a review of efficacy and a review of safety.

The efficacy portion of the review included reviews of Study VER001-9, dalbavancin versus linezolid in the treatment of cSSSI, and Study VER001-8, dalbavancin versus

cefazolin/cephalexin in the treatment of uSSSI. The efficacy portion of the review was done by Janice Pohlman, M.D.

The clinical safety information provided by Vicuron Pharmaceutical comprise their reports of deaths, SAEs, and other AEs experienced by subjects enrolled in the dalbavancin clinical development program. The program consists of Phase 1 through 3 studies which evaluated the results in subjects who received intravenously administered dalbavancin (VER001).

The overall study scheme reviewed for safety was as follows:

Phase 1
Received dalbavancin = 141 subjects (3 received 3 extra doses in study 11).
Received placebo = 19 patients

- Four studies in healthy subjects (VER001-1, 2, 10 and 19)
  VER001-1 and VER001-2 studies (Phase 1) had Placebo Arms.
- Three studies in special populations:
  - 27 subjects with impaired hepatic status (VER001-12)
  - 43 subjects with impaired renal status (VER001-3, 11 and 13)
    In study VER001-3, only 3 subjects received dalbavancin, each at a single dose of 70 mg. The sponsor prematurely terminated the study to proceed to a higher more clinically relevant dose.

Phase 2: Open label comparative studies
Received dalbavancin = 81 patients
Received comparator = 55 patients

- One study involved patients with catheter-related bloodstream infection (BSI) (VER001-4)
- The second study was in patients with SSSI (VER001-5)

Phase 3: Double-blinded comparative studies = VER001-8 and VER001-9, Open label comparative study = VER001-16
Received dalbavancin = 1045 patients
Received comparator = 518 patients

- Double-blinded study in patients with uSSSI (VER001-8)
- Double-blinded study in patients with cSSSI (VER001-9)
- Open label, comparative study including patients with MRSA in both uSSSI and cSSSI (VER001-16)

The safety portion of the review was done by Menfo Imoisili, M.D., M.P.H.

The completion of the review, including collating the efficacy review and summary and conclusions from the safety review, was done by Janice Pohlman, M.D.

4.4 Data Quality and Integrity

A blinded review of electronic CRFs (eCRFs) was performed for 107 patients in VER001-9 (12.5% of the Applicant's ITT population) and 54 patients in VER001-8 (9.8% of the Applicant's ITT population). The purpose of the CRF review was to ensure that there was adherence to the protocol definitions for analysis populations and outcomes in the analysis of the study results and that data in the datasets accurately reflected the information collected in the CRF. The majority of differences between Applicant and FDA assessment were related to application of definitions described in detail at the end of Section 6.1.3.6 Statistical Methods and in Section 6.1.4.2 Efficacy Analysis Populations.

Sporadic discrepancies were noted between what was recorded on the eCRF versus site representative responses to study monitor queries in the audit trail for the eCRF. An example from Study VER001-9 is a patient eCRF indicating receipt of >24 hours of amoxicillin prior to study drug initiation that should have been an exclusion criterion and required a waiver for study entry versus the investigator response to study monitor query in the audit trail that indicated <24 hours of amoxicillin was administered. This type of discrepancy appeared to be random and infrequent.

A discrepancy noted in Study VER001-8, where treatment could be administered for 7 or 14 days, occurred when an investigator assessed the patient as requiring a second week of antimicrobial therapy, but the patient did not receive a Day 8 dose of IV study medication. The patient was included in the 14 day treatment group in the subgroup analysis, although the patient (randomized to dalbavancin) received only 7 days of treatment. It is not known whether other patients may have been similarly affected, but the net effect of not receiving the Day 8 dose of IV medication would be expected to impact the dalbavancin response rates negatively, since the Day 8 dose was active drug (versus placebo in the comparator arm).

DSI inspections were performed at three investigative sites for Study VER001-9. No inspections were performed for VER001-8, although most investigators participating in Study VER001-9 also participated in VER001-8. During the course of the inspections, it was noted that the principal investigator for one of the sites (025) was also acting as principal investigator at another site (032) not initially selected for inspection; this site was subsequently included in the inspection process. Sites were chosen for inspection based on the number of patients enrolled and number of indeterminate outcomes observed.

The following table lists the site, along with the number and percent of patients completing the study and meeting the criterion for clinical evaluability relative to the number of patients in the ITT population at that site.

Table 13: DSI Inspection Sites

Investigator Name (Site Number)	Location	Patients Applicant ITT N	Patients Completing Study n/N (%)	Patients Clinically Evaluable n/N (%)
O'Riordan (005)	National City, CA	102	86 (84.3)	80 (78.4)
Schechter (025)	Escondido, CA	78	62 (79.5)	55 (70.5)
Schechter (032)	Poway, CA	32	28 (87.5)	24 (75)
Haidar (037)	Picayune, MS	46	33 (71.7)	27 (58.7)
VER001-09 Clinical Study Report: Section 14.1 Demographic Data, Table 1.3				

Study medication dosing errors and medication dispensing errors (both active drug and placebo) were noted at all sites. A detailed description of these errors is included in this review in Section 6.1.3.4 Study Treatments Administered, Drug Accountability and Compliance Assessment, as well as the Clinical Inspection Summary by Mathew Thomas, M.D. (DSI). VAI (Voluntary Action Indicated) letters were issued to the three investigators noted above.

4.5 Compliance with Good Clinical Practices

For the clinical studies included in this NDA, the Applicant states that the studies were conducted in accordance with ethical principles of Good Clinical Practice (GCP) as required by major regulatory authorities, and in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH). Protocols, amendments, informed consent documents, and all relevant supporting data received approval from an institutional review board (IRB) or independent ethics committee (IEC) before study initiation. Informed consent was obtained from all patients or legally authorized representatives prior to study participation.

4.6 Financial Disclosures

The Applicant notes in the NDA cover letter that "All Vicuron sponsored studies collected financial disclosure information and the appropriate financial forms FDA 3454 and FDA 3455 have been provided." An electronic link to "Financial Information Item 19" is provided. This link contains FDA Form 3454 signed by Timothy J. Henkel, M.D., Ph.D., Executive Vice President and Chief Medical Officer of Vicuron. Specifically, Box 1 certifying that the Sponsor did not enter into any financial relationships with the listed clinical investigators, clinical investigators did not disclose that they had any proprietary interest in the product or significant equity in the Sponsor, and that no listed investigator received significant payments of the sort defined in 21 CFR 54.2(f) was checked. A list of investigators participating in the clinical trials is also provided.

5 CLINICAL PHARMACOLOGY

For a detailed discussion of clinical pharmacology issues, please refer to the Clinical Pharmacology review by Charles Bonapace, PharmD.

5.1 Pharmacokinetics

Dalbavancin consists of a mixture of 5 closely related homologues (A_0, A_1, B_0, B_1, and B_2) that share the same core structure. The homologues are all microbiologically active, with two homologues, B_0 and B_1, making up approximately (b) (4) of the drug product.

Dalbavancin follows linear pharmacokinetics, with a terminal elimination half-life of 321 hours when administered to healthy subjects. The mean central and peripheral volumes of distribution were 28% and 67% higher, respectively in patients with infections compared to healthy subjects. The mean plasma clearance was 43% higher in patients with infections compared to healthy subjects.

Dalbavancin is reversibly bound to plasma proteins, primarily albumin, with a mean plasma protein binding of approximately 93%. The mean percent penetration of dalbavancin in skin blister fluid was 60%.

Based on *in vitro* assays using human microsomal enzymes, dalbavancin is not a substrate or inhibitor of cytochrome P450 isoenzymes. Based on this finding, the Applicant did not perform any clinical drug-drug interaction studies. Administration of concomitant medications with known cytochrome P450 inhibitors, substrates, and inducers, did not alter dalbavancin pharmacokinetics in a clinically significant fashion. A minor metabolite, OH-dalbavancin, was observed in the urine of healthy subjects, but was below the lower limit of quantitation in plasma.

Dalbavancin is excreted in both urine and feces. Following a single dose of 1000 mg of dalbavancin, 27-45% of the administered dose was excreted in urine whereas 20% of the dose was excreted in the feces.

The effect of age, race, and gender on the pharmacokinetics of dalbavancin was evaluated in the population pharmacokinetic analysis. No appreciable differences in pharmacokinetic parameters were noted based on age (18-93 years), race, or gender.

The impact of mild, moderate, and severe renal impairment, as well as end-stage renal disease (ESRD), on the pharmacokinetics of dalbavancin was assessed in three Phase 1 studies. Mean clearance of dalbavancin decreases as the extent of renal impairment increases. Dosage adjustment is recommended for patients with severe renal impairment. Dalbavancin is not appreciably removed by hemodialysis and no dosage adjustment is recommended for patients with ESRD receiving hemodialysis. For specific dose recommendations, see Section 8.3 Special Populations, Renal Impairment.

The impact of mild, moderate, and severe hepatic impairment (Child-Pugh Class A, B, or C) was assessed in a Phase 1 study. The mean exposure, as measured by the $AUC_{0\text{-}336hrs}$, decreased 28% and 31% in patients with moderate and severe hepatic impairment, respectively. No dosage adjustment is recommended for patients with mild hepatic impairment. The clinical significance of the increased clearance of dalbavancin in patients with moderate and severe hepatic impairment is unknown.

5.2 Pharmacodynamics

The mouse neutropenic thigh model of infection was studied to evaluate the association of common PK/PD parameters with *in vivo* efficacy of dalbavancin. The study demonstrated that the area under the concentration-time curve to MIC ratio (AUC/MIC) was best associated with *in vivo* efficacy for *Staphylococcus aureus*, while both AUC/MIC and peak serum concentration to MIC ratio (C_{max}/MIC) showed strong association with *in vivo* efficacy for *Streptococcus pneumoniae*. Increasing the dosing interval for drug administration required lower concentrations of drug for efficacy.

A Monte Carlo simulation using population pharmacokinetic estimates for dalbavancin concentration-time profiles and MIC distributions from Phase 3 clinical isolates was used to assess potential breakpoints for dalbavancin. Based on the Monte Carlo simulation, the Applicant is proposing a breakpoint of (b) (4) for *Staphylococcus aureus*.

5.3 Exposure-Response Relationships

A population pharmacokinetic analysis using demographic, pharmacokinetic, MIC, microbiologic efficacy, and clinical efficacy data from Phase 2 and Phase 3 clinical studies was performed. (b) (4)

6 INTEGRATED REVIEW OF EFFICACY

(b) (4)

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with Gram positive pathogens identified at the local laboratory only, consistent with usual FDA microbiology review practices. Dalbavancin demonstrated microbiological results comparable to the active comparator, linezolid.

Pathogens isolated in patients with favorable microbiological responses in sufficient numbers to support a labeling claim for cSSSI, based on the 1992 Points to Consider document, are *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates) and *Streptococcus pyogenes*. Although there were only nine *Streptococcus agalactiae* isolates in the FDA ME population, consideration should be given to including this organism in the cSSSI indication due to supporting evidence of efficacy for seven isolates in the uSSSI study (VER001-8).

7 INTEGRATED REVIEW OF SAFETY

Please refer to the Safety Review done by Menfo A. Imoisili, M.D.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The selection of a weekly dalbavancin dosage regimen was based on PK/PD data from animal models of infections and humans. Dose fractionation experiments using a neutropenic mouse thigh infection model (with S*taphylococcus aureus* and *Streptococcus pneumoniae*) demonstrated that the same total dose was more efficacious when administered as larger, less frequent individual doses than when administered as smaller, more frequent doses. (b) (4) , the Applicant discontinued the daily dose treatment arm (650 mg loading dose followed by 65 mg daily) from a Phase 2 CR-BSI study (VER001-4). In a small Phase 2 SSSI study, the Applicant demonstrated that the clinical efficacy of weekly dalbavancin (1000 mg on Day 1, followed by 500 mg on Day 8) was better than the clinical efficacy of a single dose of dalbavancin (1100 mg) for the treatment of SSSI (including both uncomplicated and complicated SSSI), with clinical response rates of 94% versus 62%, respectively.

Dose modifications for special populations are discussed in Section 8.3 below.

8.2 Drug-Drug Interactions

Based on the findings from *in vitro* metabolism studies that dalbavancin is neither an inhibitor not a substrate of cytochrome P450 isoenzymes, the Applicant did not perform any clinical drug-drug interaction studies. The Applicant did assess the effect of the administration of concomitant medications as covariates within the population pharmacokinetic analysis. No clinically relevant differences in the pharmacokinetics of dalbavancin were noted when dalbavancin was administered alone or co-administered with known cytochrome P450 inhibitors, substrates, and inducers, as well as additional drugs. For additional information, see the Biopharmaceutic

review by Charles Bonapace, PharmD. and Section 7.4.25 of the Clinical Safety review by Menfo Imoisili, M.D.

8.3 Special Populations

Age/Race/Gender

The effect of age, race, and gender on the pharmacokinetics of dalbavancin was evaluated in the population pharmacokinetic analysis. No appreciable differences in pharmacokinetic parameters were noted based on age (18-93 years), race, or gender. For additional information, see the Biopharmaceutic review by Charles Bonapace, PharmD.

Subgroup analysis of Phase 3 clinical trials in SSSI, including Studies VER001-8 and VER001-9, did not demonstrate appreciable differences in efficacy or safety based on age or gender. Clinical response rates for non-white patients (particularly Hispanics) in VER001-8 were 20% lower in the dalbavancin treatment arm but not the comparator, cefazolin, treatment arm. Similarly, clinical response rates for black patients in VER001-9 were 15-20% lower in the dalbavancin treatment arm but not the comparator, linezolid, treatment arm. The number of patients in the subgroups with the lower response rates (Hispanics in VER001-8 and blacks in VER001-9) were small, with approximately 50 and 35 patients in the ITT and CE analysis populations, respectively for these subgroups. The small numbers may partially explain the difference in response rates. Since the subgroup analyses are not powered for assessment of non-inferiority, conclusions based on these analyses should be made with caution.

No dosage adjustments based on age, race, or gender are recommended.

Renal Impairment

The impact of mild, moderate, and severe renal impairment, as well as end-stage renal disease (ESRD), on the pharmacokinetics of dalbavancin was assessed in three Phase 1 studies. Mean clearance of dalbavancin decreases as the extent of renal impairment increases. For detailed information on the impact, see the Biopharmaceutic review by Charles Bonapace, PharmD.

No dosage adjustment is recommended for patients with mild or moderate renal impairment or for patients with ESRD receiving hemodialysis. Dalbavancin was not appreciably removed after 3 hours of hemodialysis. No data are available on dalbavancin concentrations in patients receiving peritoneal dialysis. Based on simulated individual concentration-time profiles from subjects with normal renal function and mild, moderate, and severe renal impairment, the proposed dosage regimen for patients with severe renal impairment is 750 mg on Day 1 and 375 mg on Day 8.

Hepatic Impairment

The impact of mild, moderate, and severe hepatic impairment (Child-Pugh Class A, B, or C) was assessed in a Phase 1 study. The mean exposure, as measured by the $AUC_{0\text{-}336hrs}$, decreased 28% and 31% in patients with moderate and severe hepatic impairment, respectively. For detailed information on the impact, see the Biopharmaceutic review by Charles Bonapace, PharmD.

No dosage adjustment is recommended for patients with mild hepatic impairment. The clinical significance of the decreased exposure to dalbavancin in patients with moderate and severe

hepatic impairment is unknown. Caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic impairment as no data are available to determine the appropriate dosing.

Pregnancy
In rats, with plasma exposures approximately $1/10^{th}$ of human exposure, delayed fetal maturation, increased embryo-lethality, and increased deaths during the first week post-partum were observed. In rabbits, doses of 15 mg/kg (approximately $3/10^{th}$ of the recommended human dose on a body surface area basis), showed no evidence of embryo/fetal toxicity. For further information on animal studies in pregnancy, see the Pharmacology/Toxicology review by Wendelyn Schmidt, Ph.D.

Use of dalbavancin in pregnant women has not been studied.

Dalbavancin has been classified as Pregnancy Category C. Dalbavancin should be used only during pregnancy if the potential benefit justifies the potential risk to the fetus.

Lactation
Dalbavancin is excreted in the milk of lactating rats. It is not known whether dalbavancin or its metabolite is excreted in human milk.

8.4 Pediatrics

At the End of Phase 2 Meeting held with the Applicant and the Division on October 30, 2002, the Pediatric Rule was not in effect and discussion of the pediatric study plan was deferred. At a Pre-NDA Meeting on May 11, 2004, the Division asked the Applicant to conduct a safety study in juvenile animals prior to initiating safety and pharmacokinetic studies in children. The Applicant submitted a Pediatric Deferral Request to the Division on November 9, 2004 (IND 60,613, N-188). As stated in the NDA Review Classification Status Letter from the Division to the Applicant on February 23, 2005, a deferral was granted for completion of pediatric studies until December 31, 2009, along with a request for the pediatric development plan to be submitted to the Agency within 120 days of the letter.

(b) (4)

(b) (4)

[redacted]

8.5 Advisory Committee Meeting

No Advisory Committee Meeting was convened for this review.

8.6 Literature Review

There was no formal review of literature undertaken for review purposes for this NDA. Literature references were cited in both the efficacy and safety portions of the review and are appropriately noted.

8.7 Postmarketing Risk Management Plan

Postmarketing risk management activity must include postmarketing reporting of adverse drug experiences as outlined in 21 CFR 314.80. Prescribing clinicians should be informed through product labeling of the abnormalities in liver function tests and abnormal glucose levels noted in dalbavancin-treated patients relative to comparator-treated patients in Phase 3 clinical trials. Consideration should be given to monitoring for *in vitro* resistance of clinical microbiology laboratory isolates to dalbavancin.

8.8 Other Relevant Materials

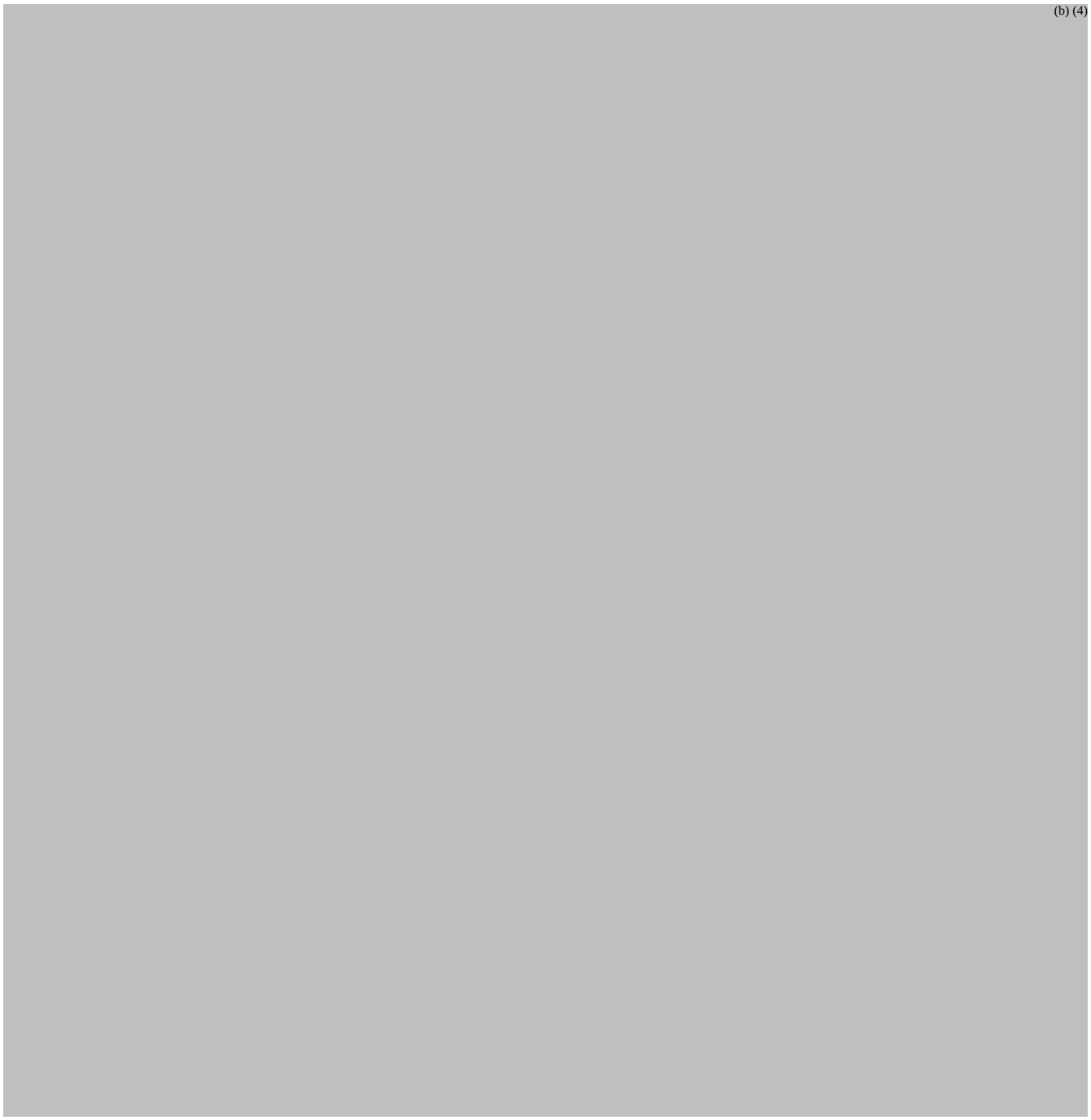
There are no other relevant materials pertinent to this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Medical Officer Efficacy Conclusions:

(b) (4)



Medical Officer Safety Conclusions:
Based on the analyses of the data reviewed, the Medical Reviewer is able to make the following safety conclusions:

- The most common toxicities in dalbavancin-treated patients were related to the gastrointestinal (GI) tract: nausea, diarrhea, vomiting and constipation. These adverse events in dalbavancin-treated patients occurred at frequencies that were similar to the patients who received comparator. They were mostly mild to moderate in severity, and resolved within a median duration of 3 days.

- Headache and pyrexia occurred with comparable frequencies in the two treatment arms. They were also mild to moderate in severity and generally resolved within about 3 days.

- Of the deaths that occurred in patients who received dalbavancin, none appeared to be causally associated with the receipt of dalbavancin. The rates of deaths in those who received comparator were similar.

- The rates of serious adverse events (SAEs) in patients that received dalbavancin were also similar to the rates in patients who were comparator-treated. Aside from one case of leukopenia which resolved within 29 days, no other causal relationship could be determined between the receipt of dalbavancin and any other SAE.

- Animal toxicology data revealed the following toxic effects in rats and dogs that received dalbavancin for up to 3 months duration:
    - Persistent liver enzyme (AST/ALT) elevations
    - Hepatocellular necrosis/ vacuolization/degeneration
    - Pancreatic (acinar cells) vacuolization/degeneration/ apoptosis
    - Persistent elevations in Blood Urea Nitrogen (BUN)
    - Renal tubular vacuolization/degeneration/ necrosis
- And the following affected dogs only:
    - Persistent RBC decreases (up to one year post-dose)

- In screening for possible safety signals and based on laboratory data reviewed, the following were found:

    - **Liver**
      Although the rates of ALT/ AST elevations < 20 x Upper Limit of Normal (ULN) were comparable across study arms, the contribution of dalbavancin to liver enzyme elevations >20 x ULN could not be excluded in two cases.

    - **Pancreas**
      Hypoglycemia
      Five dalbavancin-treated patients in studies 8 and 9, one of whom was diabetic, developed clinically significant hypoglycemia (i.e., glucose level of < 40 mg/dL). They were reported to be asymptomatic. By comparison, no patient who received comparator treatment in the same studies developed hypoglycemia. Two patients in Phase 1 also developed clinically significant hypoglycemia.

Hyperglycemia
Six dalbavancin-treated patients had hyperglycemia compared to one comparator-treated patient in studies 8 and 9. However, four of the six dalbavancin-treated patients with hyperglycemia were diabetic.

In addition, three other hyperglycemic cases were found with one case in each of Studies 16 (Phase 3), 5 (Phase 2), and 11 (Phase 1). These numbers are too small to enable assessment of their clinical significance. The issue is also confounded by the presence of diabetes mellitus. Although the animal pancreatic toxicity did not involve the islet cells, these findings are noteworthy. There were no amylase or lipase results in the database.

- **Kidney**
  There were no safety signals detected at this time in the data reviewed. The elevations in BUN and creatinine were comparable across study arms. No outliers in these laboratory parameters were seen at this time.

- **Hematology**
  The frequencies of anemia were similar across study arms. No outliers or abnormal trends were found.

- There were a few QTcB abnormalities, including one notable outlier who received dalbavancin and had a post baseline QTcB of 95 msec. The test was never repeated and therefore it remains unknown if the abnormality was clinically significant.

- The safety implications of prolonged or repeated use of dalbavancin could not be evaluated in this review. Post marketing surveillance may provide useful information in this area.

The relatively small size of this database (in the order of 1,000) could have limited the reviewer's ability to detect rare adverse events. Although the overall population may have been acceptable for this review, a larger size of study population may have allowed for a fuller and more comprehensive characterization of the safety profile of dalbavancin. Post-marketing surveillance may provide such additional information.

In summary, the sponsor has demonstrated an acceptable safety profile for dalbavancin for the indication of cSSSI for which efficacy has been demonstrated. The safety profile is adequate to support approval. However, a satisfactory post marketing surveillance is advised to detect any possible safety signal obscured by a fairly limited database.

The sponsor has also demonstrated that, when used for the treatment of cSSSI, dalbavancin is as safe as the antimicrobial products to which it was compared in the studies conducted.

9.2 Recommendation on Regulatory Action

- The Applicant has submitted a single adequate and well-controlled study with 854 patients demonstrating that dalbavancin administered intravenously at a dose of 1000 mg

on Day 1 followed by a 500 mg dose on Day 8 is noninferior to intravenous/oral linezolid 600 mg q 12 hrs for the treatment of cSSSI due to susceptible strains of *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, and *Streptococcus agalactiae*. The efficacy findings for this study are supported by the demonstration of noninferiority in a Phase 3 trial of intravenous dalbavancin 1000 mg on Day 1 with the option of a second 500 mg dose on Day 8 versus IV cefazolin 500 mg q 8 hrs/oral cephalexin 500 mg QID for 7 or for 14 days for the treatment of uSSSI. Based on the evidence from the cSSSI trial, along with supportive evidence from an uSSSI trial, there is adequate efficacy data to recommend approval.

- From the safety standpoint, the reviewer recommends approval of dalbavancin for the treatment of cSSSI based on the risk/benefits assessment. No systemic flaws identified had significant adverse impact on the study outcome or goal. The weaknesses in the process were mitigated by the good results and the value of the product, including the convenience of dosing and the drug's efficacy against potentially life-threatening diseases caused by resistant Gram positive pathogens involved in SSSI.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Postmarketing risk management activity must include postmarketing reporting of adverse drug experiences as outlined in 21 CFR 314.80. Prescribing clinicians should be informed through product labeling of the abnormalities in liver function tests and abnormal glucose levels noted in dalbavancin-treated patients relative to comparator-treated patients in Phase 3 clinical trials. Consideration should be given to monitoring for *in vitro* resistance of clinical microbiology laboratory isolates to dalbavancin.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments related to clinical issues.

9.3.3 Other Phase 4 Requests

Based on abnormal glucose levels (both low and high) observed in dalbavancin-treated patients during clinical trials, a study designed to explore the effect of dalbavancin administration on glucose homeostasis and relationship of glucose levels to dalbavancin pharmacokinetic parameters is recommended. Assessment in both diabetic and non-diabetic patients is recommended and could be performed in conjunction with a dalbavancin efficacy trial in treatment of infected ulcers and other deep (non-cellulitis) soft tissue infections.

9.4 Labeling Review

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10 APPENDICES

10.1 Review of Individual Study Reports

(b) (4)

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/s/

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