FDA BRIEFING DOCUMENT

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

MARCH 31, 2014

AFTERNOON SESSION

NDA 21-883: Dalvance (Dalbavancin) for Injection

APPLICANT: Durata Therapeutics, Inc.

PROPOSED INDICATION:

Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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INTRODUCTION

This briefing document describes the review of safety and efficacy data for dalbavancin, prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. We would like the committee to discuss whether the data are adequate to support safety and efficacy of dalbavancin for ABSSSI.

We are also interested in any other issues the committee considers relevant.

1 DALBAVANCIN PRODUCT INFORMATION

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

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

Because of its long elimination half-life, the proposed dosing regimen is 1000 mg on Day 1 and 500 mg on Day 8, administered intravenously (IV).

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 DALBAVANCIN CLINICAL DEVELOPMENT AND REGULATORY HISTORY

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 in uncomplicated skin and skin structure infections requiring parenteral therapy (VER001-8). Pfizer subsequently withdrew NDA 21-883.

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 briefing document. To date, dalbavancin has not been authorized for marketing in any country.

3 CLINICAL PHARMACOLOGY

3.1 Summary of Pharmacokinetic (PK) Characteristics

3.1.1 General PK characteristics:

Dalbavancin mean Cmax 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. **Table 1** presents dalbavancin PK parameters following administration of a single IV 1000 mg dose in healthy subjects. The mean plasma concentration-time profile for dalbavancin at the recommended dosage regimen is shown in Figure 1. In patients with infections, the mean CL and central volume of distribution (Vc) were 43% and 28% higher than those in healthy subjects, respectively.

Table 1: Dalbavancin Pharmacokinetic Parameters in Healthy Subjects

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

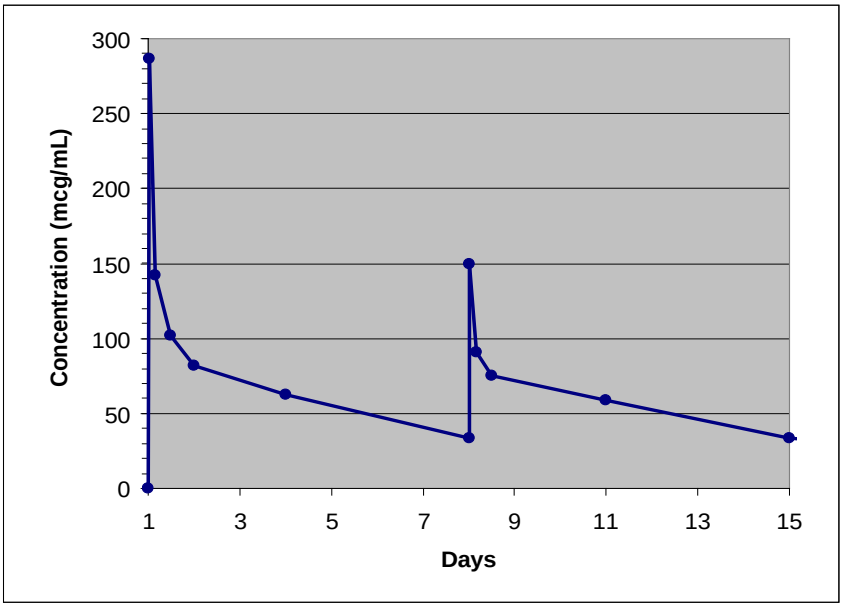
All values are presented as mean (% coefficient of variation)

[1] Data from 50 healthy subjects.

[2] Data from 12 healthy subjects.

[3] Based upon population pharmacokinetic analyses of data from patients, the effective half-life ($t_{1/2}\beta$) is approximately 8.5 days (204 hours).

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



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 assessed in six healthy subjects 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% based on $AUC_{0\text{-}7days}$ (blister fluid)/$AUC_{0\text{-}7days}$ (plasma).

Metabolism

In vitro studies using human microsomal enzymes demonstrated that dalbavancin was not a substrate or inhibitor of cytochrome P450 (CYP450) isoenzymes. A study in rats receiving 10 mg/kg/day dalbavancin for 7 days showed no induction of any CYP450 isoenzyme. 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.

Population Pharmacokinetic (PK) Analysis

A total of 1668 dalbavancin concentrations from 532 subjects from three Phase 2/3 studies were included in the population PK analysis. The plasma concentration-time profile of dalbavancin can be described using a three-compartment model with a zero order input and first order elimination. The estimated population mean for total clearance (CL) was 0.046 L/hr and the population mean for Vss was 20.85 L. Body surface area (BSA) and creatinine clearance (CrCl) were the most influential covariates, with BSA included on CL, volumes of central (Vc) and peripheral compartments (Vp1) and CrCl included on CL. Albumin, gender, and age were also important covariates but not considered to be as clinically important as BSA and CrCl.

3.1.2 Intrinsic Factors

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 of age, 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 single 30-min IV infusion 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

The impact of mild, moderate, and severe renal impairment as well as end-stage renal disease (ESRD) on the PK of dalbavancin was assessed in three clinical studies. Mean CL was 11% and 35% lower and mean AUC_{inf} was 10% and 53% higher in subjects with mild and moderate renal impairment, respectively, compared to subjects with normal renal function. Among subjects with severe renal impairment, mean CL was approximately 50% lower and mean AUC_{inf} approximately 100% higher compared to subjects with normal renal function. Mean CL was 39% lower in subjects with ESRD compared to subjects with normal renal function when dalbavancin was administered prior to hemodialysis, whereas the mean CL was 19% lower when dalbavancin was administered following hemodialysis. Mean AUC_{inf} was 62% and 28% higher for subjects with ESRD receiving dalbavancin pre-dialysis and post-dialysis, respectively, compared to subjects with normal renal function. After correction for body weight, dalbavancin CL (L/hr/kg) was approximately 20% lower for both groups of ESRD subjects compared to subjects with normal renal function.

Dalbavancin was not appreciably removed after 3 hours of hemodialysis. No dosage adjustment is recommended for patients with mild or moderate renal impairment and ESRD. 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 Cmax and AUC_{inf} were similar in subjects with mild hepatic impairment compared to control subjects. However, mean Cmax (day 1) and AUC_{inf} were 18% and 30% lower, respectively in subjects with moderate hepatic impairment and 29% and 36% lower, respectively in subjects with severe hepatic impairment, compared to subjects with normal hepatic function. Mean CL was 39% and 58% higher in subjects with moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic impairment. The mean elimination half-life of dalbavancin remained unchanged. A dose adjustment is not proposed for subjects with hepatic impairment.

3.1.3 Extrinsic Factors

Drug-Drug Interactions

In vitro metabolism studies show that dalbavancin is neither an inhibitor nor a substrate of CYP450 isoenzymes. No clinical drug-drug interaction studies were conducted.

3.2 Pharmacokinetics/Pharmacodynamics

Animal Models of Infection

The unbound AUC_{0-24} hours 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. An unbound AUC/MIC associated with a static effect against *S. pneumoniae* and *S. aureus* were 17.6 ± 6.9 and 265 ± 143, respectively.

Cardiovascular effects

A thorough QT study was conducted in healthy adults with a single supra-therapeutic dose of IV dalbavancin (1500 mg). Based on applicant's assessment a small, concentration-dependent effect of dalbavancin on the placebo-corrected, change-from-baseline in QTcF (ΔΔQTcF) was identified with an estimated slight negative population slope of -0.0051 msec/mcg/mL and a zero intercept. The results demonstrated that dalbavancin did not affect the QTc interval in a clinically relevant way.

4 MICROBIOLOGY

Dalbavancin is active against Gram-positive bacteria including methicillin-sensitive and methicillin-resistant *S. aureus* (MRSA), streptococci, enterococci, and 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 coryneform bacteria.

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 *Lactobacillus*, *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, dalbavancin is active against VanB and VanC enterococci. In these vancomycin-resistant organisms, dalbavancin does not induce the expression of altered dipeptide, nor does it have sufficient affinity for another modified peptide terminus, D-alanyl-D-serine.

Dalbavancin minimum inhibitory concentrations 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*).

5 NONCLINICAL 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

Fetal loss 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 manifests in maternal toxicity. No evidence of teratogenicity associated with dalbavancin was demonstrated in rats or rabbits.

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 necessary for this drug as use is short term.

6 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 2**.

Table 2: 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					

The efficacy and safety evaluations focus on the two most recent phase 3 trials, DUR001-301 and DUR001-302. Aggregate safety analyses of all seven phase 2 and 3 trials were also conducted, the source of this safety data is depicted in **Table 3**. In addition, safety analysis of selected Phase 1 trials, for instance a thorough QT study was conducted and Phase 1 safety datasets were searched for adverse events of interest.

Table 3 : 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 (cSSSI)	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					

6.1 OVERVIEW OF TRIALS DUR001-301 AND DUR001-302

These two phase 3 trials compared efficacy and safety of dalbavancin to the comparator regimen of vancomycin (with optional switch to oral linezolid) for the treatment of ABSSSI.

6.1.1 Study Design

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 duration of treatment ranged from 10 to 14 days. 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. The noninferiority margin was 10%.

6.1.2 Enrollment Criteria

Enrollment of patients with major abscesses was capped at 30%. In addition, at least 40% of patients in trial DUR001-301 and 25% of patients in trial DUR001-302 were to have fever at baseline.

Key Inclusion Criteria

1. Male or female patients 18 to 85 years of age having an ABSSSI that is suspected or confirmed to be caused by Gram-positive bacteria:
   a. Major cutaneous abscess 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 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.
      - Cellulitis associated with erythema that involved at least 75 cm^2 of surface area, or cellulitis of the central face that was associated with an affected area of at least 50 cm^2.
2. 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

3. Patients must have presented with at least one of the following systemic signs of infection:
    - An elevated body temperature ≥38°C/100.4°F within 24 hours of baseline
    - White blood cell (WBC) count >12,000 cells/mm^3 or WBC differential count with ≥10% band forms
4. Infection severity such that a minimum of 3 days of IV therapy was appropriate for management of the ABSSSI.

Key Exclusion Criteria

1. Receipt of a systemically or topically administered antibacterial drug 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.
2. Infection due to an organism known prior to study entry to be resistant to dalbavancin or vancomycin (vancomycin mean inhibitory concentration >8 μg/mL).
3. 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.
4. 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.
5. Venous catheter entry site infection.
6. Infections that involved diabetic foot ulceration, a perirectal abscess or a decubitus ulcer.
7. Patient with an infected device, even if the device was removed.
8. 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.
9. Patients whose ABSSSI was the result of having burns.
10. Patients with ABSSSI such as superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that only required surgical drainage for cure.
11. Anticipated need of antibacterial drug therapy for longer than 14 days.
12. 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.
13. Absolute neutrophil count <500 cells/mm^3.
14. Known or suspected HIV infected patients with a CD4 cell count <200 cells/mm^3 or with a past or current acquired immunodeficiency syndrome (AIDS)-defining condition.
15. Patients who were receiving oral steroids >20 mg prednisolone per day (or equivalent) or receiving immunosuppressant drugs after organ transplantation.
16. 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.

6.1.3 Study Procedures

In the dalbavancin arm, subjects received a single dose of dalbavancin on Day 1 and a second single dose of dalbavancin 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 between 3 and 14 days. An IV placebo infusion was given on Days 1 and 8 to match the dalbavancin dosing regimen.

Following at least 72 hours of study treatment, subjects may have been switched to oral therapy (linezolid 600 mg q12h for subjects in the vancomycin/linezolid group or matching placebo for 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 is improvement in some and no worsening in any of the clinical signs of the ABSSSI

Subjects on oral therapy still receive the placebo or dalbavancin infusion on Day 8.

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

6.1.4 Antibacterial Drug Dosage

Dalbavancin doses were 1000 mg on Day 1 and 500 mg on Day 8 for subjects with creatinine clearance (CrCl) ≥30 mL/min and those receiving hemodialysis or peritoneal dialysis. Subjects with a CrCl <30 mL/min and not on dialysis received dalbavancin 750 mg on Day 1 and 375 mg on Day 8.

Vancomycin was administered at 1000 mg or 15 mg/kg (depending on the study site standard of care) every 12 hours to subjects with normal renal function. Subjects with impaired renal function had their dosage adjusted by an unblinded pharmacist. Oral linezolid was given at 600 mg q12h.

6.1.5 Outcome Measures

The primary efficacy outcome measure was Early 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 ITT population. Patients with missing data or lost to follow-up were classified as non-responders.

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

Clinical success at EOT 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 one 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

6.1.6 Statistical Methods

Applicant's Primary Analysis

The primary efficacy analysis was performed in the ITT population. The NI test was a 1-sided hypothesis test performed at the 2.5% level of significance and was based on the lower limit of the 2-sided 95% confidence interval (CI). The primary efficacy outcome measure was clinical response (cessation of spread of lesion, and the absence of fever) at 48 to 72 hours. Patients who met these criteria were classified as responders. However, 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 adjusted for the randomization stratification factor of presence or absence of fever at baseline.

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

H_0: $p_1 - p_2 \leq -\Delta$
H_1: $p_1 - p_2 > -\Delta$

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

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

The 2-sided 95% CI for NI testing based on the difference of clinical response rates at 48 to 72 hours was computed using the method proposed with stratification by Miettinen and Nurminen (Miettinen 1985).

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

The sample size was increased only in Study DUR001-302 from an initially planned number of 556 subjects to approximately 740 subjects. This increase was based on the overall response rate observed at the interim analysis (i.e. 78.7%) which fell below the assumed rate of 85%. In order to maintain study power at 90%, the DMC had recommended that the sample size be increased to 740 subjects. The actual number of ITT subjects in Study DUR001-302 was 739.

Missing Data: For the primary outcome measure (clinical response at 48 to 72 hours), the patient was considered to have missing data if there was no lesion measurement at baseline and/or in the 48 to 72 hour (after first dose of study drug) time period. In addition, the patient was considered to have missing data if there were not 3 temperature measurements in the 48 to 72 hour time period taken 6 hours (±3 hours) apart. Patients with missing data were defined as a non-responder for the primary analysis (ITT analysis).

FDA Reviewer Analyses

Statistical methodologies used in the FDA Reviewer primary analyses were similar to those of the applicant. In the FDA Reviewer's analyses, clinical response (responder) rates were evaluated using the lower 95% confidence limit of the treatment difference ('dalbavancin' minus 'vancomycin/ linezolid').

FDA Reviewer analyses also considered responder rates at 48-72 hours (Day 3) in which responders were defined as those patients achieving at least a 20% reduction in lesion area as a key secondary analysis, as per the current guidance for ABSSSI. [1] Similar to the pre-specified primary endpoint, additional analyses of responders based on 20% reduction in lesion area were performed.

Additional sensitivity analyses of interest included the following:

- Clinical Status at end of treatment (EOT, Day 14-15) in the ITT population, with stricter requirements for reductions in lesion area, such as 80% and 90% reduction in the ITT population
- Complete resolution of local signs and symptoms at SFU at Day 26-30, with and without allowance of 10% residual erythema in the ITT population
- Success/resolution rates at EOT/SFU by responder status at 48-72 hours (Concordance)
- Changes in the % reductions in erythema

In the above analyses, patients with missing data at the specified visit were considered non-responders (failures) or assigned the least favorable categorical outcome in the case of non-binary data (e.g. percentage reduction in lesion area).

7 EVALUATION OF EFFICACY

Efficacy analyses are based on the results of trials DUR001-301 and DUR001-302.

7.1 Subject Demographics and Disposition

Demographics and baseline characteristics in trials DUR001-301 and -302 are presented in **Table 4**.

Table 4: Demographic and Baseline Characteristics in DUR001-301 and -302 Trials (Safety Population)

	Dalbavancin (N=652) n (%)	Comparator (N=651) n (%)
Age (years)		
Mean (SD)	48.9 (16)	50.3 (15.7)
Min, Max	18, 85	18, 84

[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

Table 4: Demographic and Baseline Characteristics in DUR001-301 and -302 Trials (Safety Population)		
	Dalbavancin (N=652) n (%)	Comparator (N=651) n (%)
< 65	546 (83.7)	527 (81)
≥ 65	106 (16.3)	124 (19)
Gender N (%)		
Male	388 (59.5)	374 (57.5)
Female	264 (40.5)	277 (42.5)
Creatinine Clearance		
< 30 mL/min	19 (2.9%)	14 (2.2%)
30-59 mL/min	121 (18.6%)	123 (18.9%)
60-89 mL/min	195 (29.9%)	191 (29.3%)
≥ 90 mL/min	304 (46.6%)	311 (47.8%)
Unknown	13 (2%)	12 (1.8%)
Baseline Hepatobiliary Status		
Elevated [a]	33 (5.1%)	39 (6%)
Not Elevated	574 (88%)	577 (88.6%)
Unknown	45 (6.9%)	35 (5.4%)
Location n (%)		
North America	233 (35.7)	234 (35.9)
Eastern Europe/South Africa	395 (60.6)	389 (59.8)
Western Europe	0	0
Asia / Pacific	24 (3.7)	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

Source: Adapted from tables 13, 15,16, 2-2.3.1, 2.-2.3.2, 2-2.4.1, and 2-2.4.2; Integrated summary of safety

Types of skin infections seen in trials DUR001-301 and -302 trials are presented in **Table 5**.

Table 5: Characteristics of ABSSSI in DUR001-301 and DUR-302 Trials (ITT population)				
	DUR001-301		DUR001-302	
	Dalbavancin N=288 n (%)	Comparator N=285 n (%)	Dalbavancin N=371 n (%)	Comparator N=368 n (%)
Infection Types				
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
Infection Area Baseline Measurements (Area cm^2)				
Cellulitis				
Median	348.5	496	452	466
Min, max	76.5, 3400	81, 3675	85, 5100	72, 3922

Table 5: Characteristics of ABSSSI in DUR001-301 and DUR-302 Trials (ITT population)				
	DUR001-301		DUR001-302	
	Dalbavancin N=288 n (%)	Comparator N=285 n (%)	Dalbavancin N=371 n (%)	Comparator N=368 n (%)
Major abscess				
Median	320	315	278	252.5
Min, max	25.6, 1390	88, 1456	110, 1007.5	80, 1813
Wound Infection				
Median	352	357	269	300
Min, max	84, 1382.5	78, 2820	88, 2006	90, 2471

In trial DUR001-301, 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 one Gram-positive ABSSSI pathogen isolated at baseline from a blood culture or from a culture from the primary ABSSSI site, as shown in **Table 6**. In trial DUR001-302, a total of 184/371 (49.6%) subjects in the dalbavancin arm and 174/368 (47.3%) subjects in the comparator arm had at least one Gram-positive ABSSSI pathogen isolated at baseline. *S. aureus* was isolated most commonly in both treatment arms and in both trials. Overall, *S. aureus* constituted about 77% of all isolates and methicillin-resistant *S. aureus* accounted for about 24% of all isolates.

Table 6: 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)
Staphylococcus aureus	122 (79.7)	128 (82.6)	135 (73.4)	128 (73.6)
MRSA	44 (28.8)	39 (25.2)	46 (25.0)	28 (16.1)
MSSA	78 (51.0)	88 (56.8)	89 (48.4)	101 (58.0)
Streptococcus pyogenes	12 (7.8)	14 (9.0)	25 (13.6)	22 (12.6)
Other Streptococcus sp.	17 (11.1)	25 (16.1)	37 (20.1)	28 (16.1)
Enterococcus faecalis	3 (2.0)	5 (3.2)	9 (4.9)	8 (4.6)
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.

MRSA – methicillin-resistant *S. aureus*: MSSA – methicillin-sensitive *S. aureus*

Source: modified from Tables 11.11, clinical study reports DUR001-301 and DUR001-302.

Study dropouts in pooled DUR001-301 and DUR001-302 trials are presented in **Table 7**. The number of subjects who discontinued from the study was similar in the dalbavancin and comparator arms, 66 (10%) and 63 (9.6%), respectively. The main reason for discontinuation was 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. The verbatim terms used under the category of "other" were also 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 7: Reasons for Study Dropouts in Pooled DUR001-301 and 302 trials

	Dalbavancin		Vancomycin	
	No. of Subjects	%	No. of Subjects	%
Informed consent obtained	659	100	653	100
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

7.2 Analysis of Primary Efficacy Endpoint

The analysis of the primary endpoint, i.e., Early Clinical Response at 48-72 hours in the ITT population, demonstrated that in both trials dalbavancin was noninferior to the regimen of vancomycin/linezolid, **Table 8**. Since the lower bound of the 95% CI 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 8: Primary Efficacy Analysis in Trials DUR001-301 and DUR001-302 (ITT)

	Dalbavancin n/N (%)	Vancomycin/Linezolid n/N (%)	Difference (95% CI)
Early Clinical Response at 48–72 hours: Responders			
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.

As shown in **Table 9**, both trials also satisfied a key secondary endpoint in which clinical response is 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. When clinical response at 48-72 hours was defined as a ≥ 20% reduction in lesion area from baseline rather than cessation of spread of lesion and absence of fever, overall response rates were approximately 6% to 9% higher in both trials. There were also changes in the point estimates for treatment difference (dalbavancin − vancomycin/linezolid) which varied between the two trials, showing a 2.5% decrease (i.e. 1.5% to -1.0%) in trial DUR001-301 and a 3.2% increase in trial DUR001-302 (i.e. -1.5% to 1.7%).

Table 9: 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%)	-1.0% (-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.

Clinical response rates at 48 to 72 hours by stratification variables used at randomization are presented for trials DUR001-301 and DUR001-302, in **Table 10** and **Table 11**, respectively. In both trials, clinical response rates were higher among patients with fever at baseline. In patients who were afebrile at baseline (approximately 18% of patients in each of the trials), treatment differences favored dalbavancin in trial DUR001-301 and the comparator in trial DUR001-302. Considering geographic region, clinical response rates were also inconsistent across trials; lower rates were observed in North America versus the rest of the world (ROW) in trial DUR001-301 but substantially higher rates were observed in trial DUR001-302.

Considering the infection types, in trial DUR001-302, higher response rates were seen among subjects with major abscesses compared to those with cellulitis and wound infections. It is not clear as to how much incision and drainage procedures may have influenced the treatment effect in this trial. Treatment differences favored dalbavancin in patients with cellulitis (trial DUR001-301) and the comparator in patients with major abscess (trial DUR001-302); however, these differences were not consistent across both trials.

Table 10: Clinical Response Rates at 48-72 hours by Stratification Variables at Randomization, Trial -301 (ITT)

Stratification Variables	Dalbavancin (N=288) n/N* (%)	Comparator (N=285) n/N* (%)	Difference (95% CI)[1]
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)

Table 10: Clinical Response Rates at 48-72 hours by Stratification Variables at Randomization, Trial -301 (ITT)			
Stratification Variables	Dalbavancin (N=288) n/N* (%)	Comparator (N=285) n/N* (%)	Difference (95% CI)[1]
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)
Infection Type			
Cellulitis	133/156 (85.3)	116/147 (78.9)	6.4 (-2.3, 15.1)
Major Abscess	58/72 (80.6)	73/86 (84.9)	-4.3 (-16.8, 7.5)
Wound Infection	49/60 (81.7)	44/52 (84.6)	-2.9 (-17.0, 11.7)
[1]95% CIs were calculated using the Miettinen and Nurminen approach, unadjusted.			

Table 11: Clinical Response Rates at 48-72 hours by Stratification Variables at Randomization, Trial -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)
Infection Type			
Cellulitis	148/198 (74.7)	153/202 (75.7)	-1.0 (-9.5, 7.5)
Major Abscess	75/90 (83.3)	76/87 (87.4)	-4.1 (-14.8, 6.7)
Wound Infection	62/82 (75.6)	59/79 (74.7)	0.9 (-12.5, 14.4)
[1] 95% CIs were calculated using the Miettinen and Nurminen approach, unadjusted.			

7.3 Analysis of Secondary Efficacy Endpoints

Analysis using the applicant's pre-specified secondary endpoint of clinical status at EOT (success/failure) in the ITT and CE-EOT populations is presented in **Table 12** along with the endpoint of clinical status at SFU in the ITT population. These endpoints served to evaluate the maintenance of the clinical response achieved at 48-72 hours at later timepoints. 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, trial DUR001-302 showed slightly higher rates of clinical response in the dalbavancin arm at the EOT and SFU visits.

Table 12: Secondary Clinical Efficacy Endpoint Analysis in Trials DUR001-301 and DUR001-302			
Endpoint Definition	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)[1]
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) [1] 95% CIs were calculated using the Miettinen and Nurminen approach, unadjusted.			

The applicant's endpoints of clinical status at EOT and SFU did not have strict requirements placed on certain signs/symptoms. For example, regarding erythema, patients needed to show only a decrease in lesion size (i.e. any magnitude of decrease). Consequently, sensitivity analyses for these endpoints considered stricter requirements for the resolution of erythema at EOT (i.e. % reduction in lesion area of 80% and 90% and an erythema rating of no worse than mild). These analyses were conducted in order to be more consistent with the requirements for responders in the key secondary analysis (i.e. at least a 20% reduction in erythema at 48-72 hours) taking into account the progression of resolution of erythema expected by the EOT visit on Day 14-15.

Sensitivity analyses also considered the SFU visit in which success was defined as complete resolution (absence) of all local signs and symptoms (i.e. purulent drainage/discharge, erythema, fluctuance, heat/warmth, swelling/induration and tenderness to palpation) with and without an allowance for mild residual erythema (no more than 10% of the lesion size at baseline). The systemic component of fever was not included in this outcome due to a substantial number of patients who were missing fever measurements at SFU. Results from these sensitivity analyses are presented in **Table 13**. These findings show that in trial DUR001-301, success rates for clinical status at EOT and complete resolution at SFU favored the comparator over dalbavancin and in trial DUR001-302 favored dalbavancin over comparator.

Findings in these analyses, however, show inconsistencies across the two trials with lower success rates for dalbavancin vs. the comparator in trial DUR001-301 and somewhat higher success rates for dalbavancin in trial DUR001-302. Overall, in these sensitivity analyses success rates at EOT/SFU tended to be less favorable in both treatment arms in both trials as stricter requirements were placed on the degree of erythema necessary to be evaluated as a success.

Table 13: Secondary Clinical Efficacy Endpoint Analysis in Trials DUR001-301 and DUR001-302 (ITT)			
Endpoint Definition	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)[2]
DUR001-301			
Clinical Success at EOT, ≥ 80% reduction in lesion area	226 (78.5)	242 (84.9)	-6.4 (-12.8, -0.1)
Clinical Success at EOT, ≥ 90% reduction in lesion area	218 (75.7)	237 (83.2)	-7.5 (-14.1, -0.8)
Complete Resolution at SFU, ≤ 10% of baseline erythema remaining[1]	229 (79.5)	241 (84.6)	-5.1 (-11.4, 1.3)
Complete Resolution at SFU	220 (76.4)	239 (83.9)	-7.5 (-14.0, -0.9)
DUR001-302			
Clinical Success at EOT, ≥ 80% reduction in lesion area	318 (85.7)	306 (83.2)	2.6 (-2.7, 7.8)
Clinical Success at EOT, ≥ 90% reduction in lesion area	309 (83.3)	299 (81.3)	2.0 (-3.5, 7.6)
Complete Resolution at SFU, ≤ 10% of baseline erythema remaining[1]	298 (80.3)	288 (78.3)	2.1 (-3.8, 7.9)
Complete Resolution at SFU	292 (78.7)	286 (77.7)	1.0 (-5.0, 7.0)

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), Patients who used non-study systemic antibacterial drugs, had a surgical intervention or died up to SFU were counted as failures (i.e. no complete resolution at SFU). Clinical successes at EOT were also required to have an erythema rating of no worse than mild.

[1] Includes patients with complete resolution or complete resolution with only mild erythema and at least a 90% reduction in lesion area from baseline.

[2] 95% CIs were calculated using the Miettinen and Nurminen approach, unadjusted.

The analyses of concordance of clinical response at 48-72 hours with clinical status at EOT are presented in **Table 14**. In trial DUR001-301, considering only responders at 48-72 hours, 34/240 (14.2%) of patients in the dalbavancin arm were clinical failures at EOT versus 20/233 (8.6%) in the comparator arm. In trial DUR001-302, 22/285 (7.7%) of patients in the dalbavancin arm were clinical failures at EOT versus 28/288 (9.7%) in the comparator arm.

Table 14: Concordance Analysis - Responder/Non-Responders at 48-72 Hours *with* Clinical Success/Failure at EOT				
	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)

Table 14: Concordance Analysis - Responder/Non-Responders at 48-72 Hours *with* Clinical Success/Failure at EOT				
	Dalbavancin	Comparator	Dalbavancin	Comparator
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 analyses of concordance of clinical response at 48-72 hours with complete resolution of local signs and symptoms at SFU are presented in **Table 15**. In trial DUR001-301, considering responders at 48-72 hours, 46/240 (19.2%) of patients in the dalbavancin arm later failed to achieve complete resolution of local signs and symptoms versus 26/233(11.2%) in the comparator arm. In trial DUR001-302, 50/285 (17.5%) of patients in the dalbavancin arm later failed to achieve complete resolution of local signs and symptoms versus 46/288 (16.0%) in the comparator arm.

Table 15: Concordance Analysis- Responder/Non-Responders at 48-72 Hours with Complete/Incomplete Resolution of Local Signs and Symptoms at SFU				
	Dalbavancin	Comparator	Dalbavancin	Comparator
Trial DUR001-301	Responders (N=240)	Responders (N=233)	Non-Responders (N=48)	Non-Responders (N=52)
Complete resolution at SFU, n (%)	194 (80.8)	207 (88.8)	26 (54.2)	32 (61.5)
Incomplete resolution at SFU, n (%)	46 (19.2)	26 (11.2)	22 (45.8)	20 (38.5)
Trial DUR001-302	Responders (N=285)	Responders (N=288)	Non-Responders (N=86)	Non-Responders (N=80)
Complete resolution at SFU, n (%)	235 (82.5%)	242 (84.0%)	57 (66.3%)	44 (55.0%)
Incomplete resolution at SFU, n (%)	50 (17.5%)	46 (16.0%)	29 (33.7%)	36 (45.0%)

The reasons for failures in subjects who responded at 48-72 hours but failed at EOT were further evaluated and are presented in **Table 16**. In trial DUR001-301, where the imbalance between dalbavancin and comparator in terms of the maintenance of clinical response was most noticeable, a total of 34 and 20 of earlier 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 drugs for ABSSSI and incomplete resolution of local signs of infection accounted for the greater number of failures at EOT among dalbavancin subjects.

Table 16: 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 till EOT	1	0	7	5

The number of subjects who responded at EOT but failed at SFU was similar in both treatment arms in both trials. The majority of clinical failures occurred because subjects were lost to follow-up, and therefore, fell under the category of indeterminate.

7.4 Outcomes in Subjects with Bacteremia

In trials DUR001-301 and DUR001-302, 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 isolates were MSSA with the exception of one MRSA isolate in each treatment group. Other pathogens included various species of streptococci and coagulase negative staphylococci.

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

Table 17: Clinical Response at 48-72 hours in Patients with Bacteremia due to Gram-positive Pathogens 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 n (%)	6 n (%)	20 n (%)	11 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 Tables 11.12 and 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 was not documented in any of the dalbavancin-treated subjects but in 3 subjects in the comparator arms.

8 CLINICAL SAFETY

8.1 Summary

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 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 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.

8.2 Methods

Safety evaluation was conducted in the safety population that included subjects who received any dose of study drug and was primarily based on the results of trials, DUR001-301 and DUR001-302. Some safety analyses were also conducted using the integrated dataset of all seven phase 2 and 3 trials. Phase 1 trials were searched for adverse events of interest.

8.3 Overall Exposure to Dalbavancin

Because of dalbavancin PK properties, a single dose of the drug provides a 7-day exposure and the proposed treatment regimen of two IV infusions, one on day 1 and the second one on day 8 provides a 14-day exposure. Therefore, subjects treated with one dose of dalbavancin were considered to have been dosed for 7 days and subjects treated with two doses of dalbavancin were considered to have been dosed for 14 days.

A total of 2085 subjects received at least one dose of dalbavancin, including 1778 subjects in phase 2 and 3 trials with 652 subjects in trials DUR001-301 and DUR001-302, **Table 18**. For the legacy phase 2 and 3 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. Nine subjects in trials DUR001-301 and DUR001-302, seven in the dalbavancin arm and two in vancomycin/linezolid arm, were randomized but did not receive study drug and were not included in the safety population.

Table 18: Subjects Received ≥ 1 dose of Study Drug in Dalbavancin Clinical Trials		
	DUR001-301 and -302	All phase 2 and 3 trials
No of Trials	**2**	**7**
Dalbavancin	652	1778
Comparator	651	1224
Total	1303	3002

The proposed treatment regimen 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 19**. In trials DUR001-301 and DUR01-302, a total of 620/652 (95.1%) subjects were exposed to 14 days and 32/652 (4.9%) were exposed to 7 days of dalbavancin.

Table 19: 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 trials DUR001-301 and DUR001-302, 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 of dalbavancin on Day 1 and 500 mg of dalbavancin on Day 8.

In trials DUR001-301 and DUR001-302, a total of 48 out of 652 dalbavancin-treated subjects received a total dose of <1500 mg. Sixteen of these 48 patients received two doses of

dalbavancin; 15 out of these 16 received a reduced first dose of dalbavancin (750 mg) due to underlying renal impairment and one patient received 500 mg of dalbavancin on Day 1 and on Day 2 in error, **Table 20**. Thirty two out of 48 subjects received a single dose of dalbavancin; all but one of these 32 patients prematurely discontinued from the trials. The remaining patient missed the second dose of dalbavancin in error.

Table 20: 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	

The comparator arms in DUR001-301 and DUR001-302 trials included subjects exposed to vancomycin only (n=100) or vancomycin and linezolid (n=551), **Table 21**. For the purpose of safety analyses, vancomycin and vancomycin/linezolid subjects were pooled.

Table 21: Comparator Drugs in Trials DUR001-301 and DUR001-302.				
	DUR001-301	DUR001-302	**Total**	
Vancomycin	66	34	**100**	**651**
Vancomycin/Linezolid	218	333	**551**	

8.4 Study Drug Discontinuations

Study drug discontinuations and deaths are presented in **Figure 1**. Categories of study dropouts and study drug discontinuations 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. Overall, the number of subjects and reasons for discontinuations were balanced between study arms.

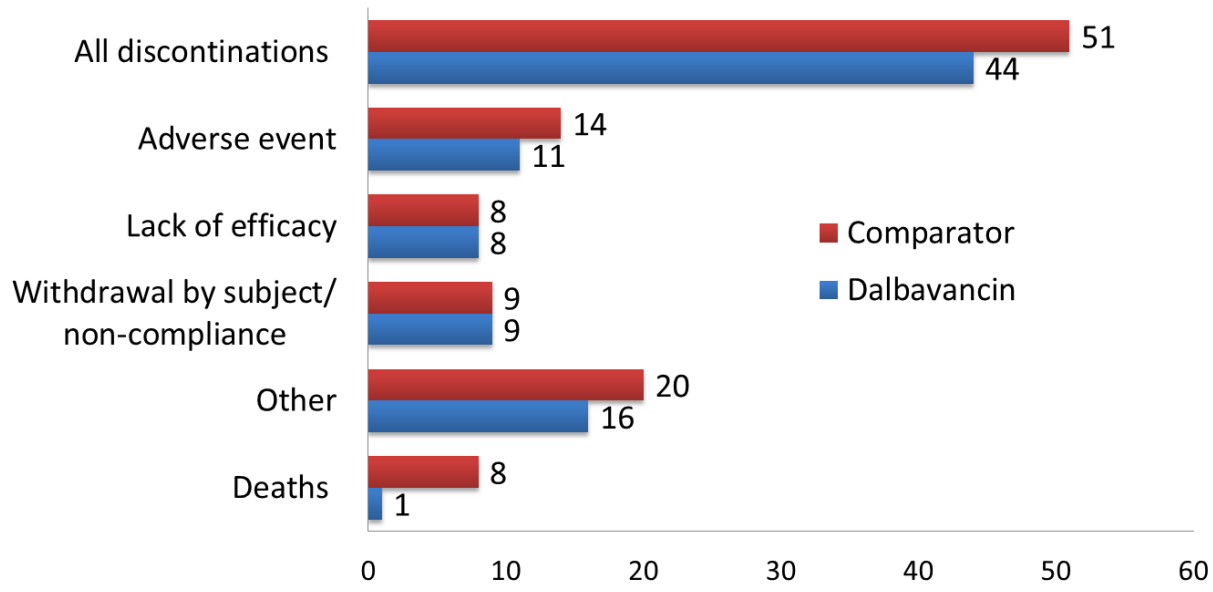


Figure 1: Study drug discontinuations and deaths

8.5 Major Safety Results

8.5.1 Deaths

All deaths occurred in phase 2 and 3 trials. Overall, there were fewer deaths in the dalbavancin group than in the comparator treated subjects, **Table 22**. No deaths were considered to be related to study drug.

Table 22: Deaths that Occurred During Dalbavancin Development Program

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

[a] DUR001-301 and -302, VER001-4, VER001- 5, VER001-8, VER001-9, and VER001-16

In trials DUR001-301 and DUR001-302, 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 23**. Two subjects in the vancomycin group died while receiving study drug. All deaths were considered unrelated to study drug.

Table 23: 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	959-277	50	M	Vancomycin	7	24	Gram-negative bacterial sepsis	Yes	Indeterminate [d]
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.*

The listing of deaths that occurred in prior trials is presented in Table 24. Most of the deaths in prior trials were related to cardiovascular diseases and there was no direct evidence for a relationship between dalbavancin and mortality in these patients.

Table 24: 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

8.5.2 Nonfatal Serious Adverse Events and Common Adverse Events

The number of subjects with nonfatal adverse events that were categorized as serious (SAE) was relatively small in both treatment groups, 17 (2.6%) in the dalbavancin and 29 (4.4%) in the vancomycin/linezolid arms. Dalbavancin treated subjects experienced a total of 19 SAEs and vancomycin treated subjects experienced a total of 35 SAEs, **Table 25**. The most common SAEs were reported under the category of infections and infestations, nine (1.4%) events in the dalbavancin arm and ten (1.5%) in the vancomycin/linezolid arm. The incidence of individual SAEs was balanced between study arms. An event of anaphylactoid reaction in a dalbavancin treated subject warrants further attention and is described in the Submission Specific Concern Section of this document.

Table 25: Selected Nonfatal Serious Adverse Events		
	Dalbavancin N=652 n (%)	Comparator N=651 n (%)
Number of subjects with nonfatal SAE	17 (2.6%)	29 (4.4%)
Number of Events	19	35
Cellulitis	3 (0.5%)	1(0.15%)
Arthritis bacterial	2 (0.3%)	0
Sepsis	1 (0.15%)	1(0.15%)
Bacterial sepsis	0	1(0.15%)
Bacteremia	1 (0.15%)	0
Embolic pneumonia	1 (0.15%)	0
Necrotizing fasciitis	1 (0.15%)	0
Gangrene	0	2 (0.3%)
Abscess / Abscess limb	0	2 (0.3%)
Diabetic foot infection	0	1(0.15%)
Appendicitis	0	1(0.15%)
Rectal abscess	0	1(0.15%)
Cardiac failure	1 (0.15%)	5 (0.8%)
Atrial fibrillation	1 (0.15%)	0
Events related to gastrointestinal disorders	2 (0.3%)	6 (0.9%)
Pulmonary Embolism	1 (0.15%)	1 (0.15%)
Cholecystitis acute	0	1 (0.15%)
Nephropathy toxic	0	1(0.15%)
Renal failure acute	0	1(0.15%)
Anaphylactoid reaction	1 (0.15%)	0

The overall incidence of adverse events reported in DUR001-301 and DUR001-302 trials was similar in the dalbavancin and comparator arms. In the dalbavancin arm, a total of 459 (70.4%) subjects experienced 617 adverse events and in the vancomycin/linezolid arm a total of 505 (77.6%) subjects experienced 698 adverse events. The most common adverse events were nausea, vomiting and headache. These events occurred at approximate rates of 4%-6% in both arms. **Table 26** presents selected common adverse events.

Table 26: Selected Adverse Events Observed in >1% of Subjects in Either Treatment Arm in Trials DUR001-301 and DUR001-302		
MedDRA Preferred Term	Dalbavancin N=652	Comparator N=651
Nausea	29 (4.4%)	32 (4.9%)
Vomiting	13 (2%)	10 (1.5%)
Headache	26 (4%)	23 (3.5%)
Diarrhea	8 (1.2%)	19 (2.9%)
Gamma-glutamyl transferase increased	13 (2%)	12 (1.8%)
ALT increased	13 (2%)	9 (1.4%)
AST increased	11 (1.7%)	2 (0.3%)
Pruritus	6 (0.9%)	18 (2.8%)
Rash	11 (1.7%)	9 (1.4%)
Pyrexia	8 (1.2%)	11 (1.7%)
Dizziness	8 (1.2%)	6 (0.9%)
MedDRA - Medical Dictionary for Regulatory Activities		

8.6 Submission Specific Safety Concerns

8.6.1 Liver Tests Abnormalities

More dalbavancin-treated subjects had significant elevations of transaminases than comparator-treated subjects. There were six subjects in the dalbavancin arm with alanine aminotransferase (ALT) elevation of greater than five times the upper limit of normal including three subjects with ALT > 10x ULN, **Table 27**. No subjects in the comparator arm had such a degree of ALT elevation.

Table 27: Hepatic Enzymes and Bilirubin 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	4.0	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

Table 27: Hepatic Enzymes and Bilirubin Elevations in DUR001-301 and DUR001-302 trials						
3x ULN	27	21	3.2	14	12	1.8
5x ULN	9	8	1.2	4	4	0.6
10x ULN	0	0	0	0	0	0
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	0.15
TB ≥ ULN						
2x ULN	3	2	0.3	3	1	0.15
3x ULN	2	1	0.15	2	1	0.15
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. There was also no imbalance between treatment arms in baseline comorbidities that may have predisposed to hepatic enzyme elevations, **Table 28**.

Table 28: 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	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 (6.25%)	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 (0.3%)	2 (0.7%)	3 (0.8%)	3 (0.8%)	4 (0.6%)	5 (0.8%)
Not all comorbidities that may have resulted in liver test abnormalities are listed and a subject may have more than one comorbidity						

Table 29 provides the number of subjects in DUR001-301 and DUR001-302 trials with normal baseline ALT and post-baseline ALT elevation of greater than 3x ULN. There were six such subjects in the dalbavancin as compared to one subject in the comparator arm.

Table 29: Shift in Alanine Aminotransferase in Subjects with Normal Baseline Transaminase Levels in Trials DUR001-301 and DUR001-302				
		Day 3 or End of Treatment		
	Baseline ALT < ULN	> 3x ULN – 5x ULN	>5x ULN – 10xULN	> 10x ULN
	N	N	n	n
Dalbavancin	518	3	1	2
Comparator	532	1	0	0

Table 30 provides shifts in ALT levels in subjects with normal baseline ALT in all phase 2 and 3 trials. Overall, there were 12 (0.8%) versus 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 30: Shift in Alanine Aminotransferase in Subjects with Normal Baseline Levels in all phase 2/3 trials					
		Post-Dose [b]			
	Baseline ALT < ULN	> 3x ULN – 5x ULN	>5x ULN – 10xULN	> 10x ULN	Total
	N [a]	n	n	n	(%)
Dalbavancin	1406	7	3	2	12 (0.8%)
Comparator	957	1	1	0	2 (0.2%)

[a] Subjects counted only once in each category; N - all subjects with normal ALT levels at baseline;
[b] For trials DUR001-301 and DUR001-302 the measurements are obtained on Day 3 and End of Treatment visits; 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 six subjects with post-baseline ALT elevation > 3x ULN in trials DUR001-301 and DUR001-302 are presented in **Table 31**. Follow-up measurements obtained in five of six 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 31: ALT Transition Profiles in Subjects with Normal Baseline ALT and Post-baseline ALT > 3x ULN in DUR001-301 and DUR001-302 Trials					
	ALT levels (normal ranges 0-45 units/L)				
Subject ID	Baseline	Day 3	EOT [a]	Day 20	Day 27-32
302-737-120	29	28	589	127	-
302-927-428	19	22	622	-	41
302-958-315	33	274	17	-	-
302-747-505	28	31	177	-	-
302-927-051	34	26	175	-	13
302-944-360	11	148	19	-	-
All subjects received 2 doses of dalbavancin [a] EOT – End of Treatment, Day 14-16					

Associated elevation in other liver tests in these subjects is presented in **Table 32**.

Table 32: Concomitant Elevation in Liver Tests in Subjects with Normal Baseline ALT and post-baseline ALT elevation > 3x ULN.

Subject ID*	Highest ALT (0-45 units/L)	AST (0-41 units/L)	TB (0.1-1.2 mg/dL)	ALP	Baseline ALP (normal ranges)
737-120	589	248	0.6	274	135 (40-129 U/L)
927-428	622	85	5.8	210	121 (35-104 U/L)
958-315	274	315	0.4	244	91 (40-129 U/L)
747-505	177	77	0.4	247	117 (40-129 U/L)
927-051	175	119	1.4	65	60 (35-104 U/L)
944-360	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; ALP – alkaline phosphatase

One subject, 302-927-428, had 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 tests for this subject are presented in Figure 2.

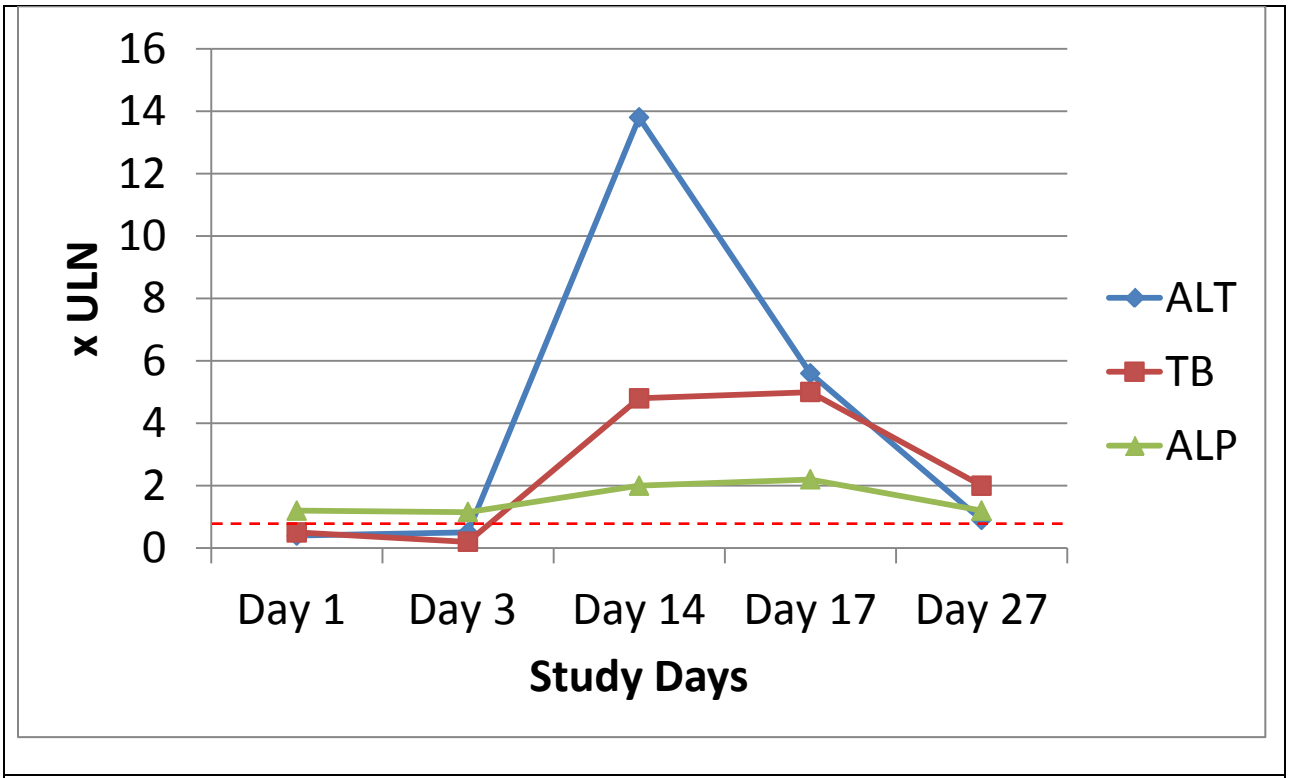


Figure 2: Liver tests in subject 302-927-428
Dashed red line indicates the upper limit of normal; TB – total bilirubin; ALP – alkaline phosphatase.

The case, however, does not meet Hy's Law criteria because of a history of hepatitis C and baseline elevation of alkaline phosphatase level[2]. In addition, the subject received ketorolac which could have also caused ALT elevation. Labeling for Ketorolac 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.

The datasets for trials DUR001-301 and DUR001-302 were also searched for subjects with post-dose elevations in either ALT or AST of ≥ 5x ULN and baseline transaminase levels < 2x ULN. There were eight such subjects in the dalbavancin arm and no subjects in the comparator group.

Overall, in trials DUR001-301 and DUR001-302, a total of 10 dalbavancin subjects had either ALT elevation > 3x ULN and normal baseline transaminases (n=6) or transaminase elevation ≥ 5x ULN with baseline transaminases < 2x ULN (n=8, including 4 subjects with normal baseline transaminases). Only one subject in the comparator arm met these criteria. ALT rose concomitantly with AST in the majority of subjects and with ALP in four subjects (ALP elevation was defined as ALP >2x ULN with no significant elevation at baseline). None of these

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

ten subjects with significant ALT elevations developed eosinophilia, so there is no basis to suspect eosinophilic hepatitis, which may occur in response to some antibacterial drugs.

Abnormalities in liver tests were documented to be resolved or significantly improved in eight out of ten subjects; two subjects did not have follow-up measurements. Of note, two out of three subjects with transaminase elevations at Day 3 demonstrated resolution of liver tests abnormalities at the EOT while continuing to receive dalbavancin. One of these three 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 eight out of ten subjects had a history of either of hepatitis C or chronic hepatitis B or alcohol abuse; in addition, one subject had a history of current or recent IV drug use. Six out of ten subjects received medications such as ketorolac, acetaminophen, carbapenems, betaxolol, and ropivacaine that could have could have contributed to liver tests abnormalities.

There were two more dalbavancin-treated subjects with significant post-baseline elevations of liver 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 one dose of dalbavancin. Baseline and end-of treatment liver tests were within normal limits, **Table 33**.

Table 33: Liver Tests of Subject VER001-8-206-017 Who Experienced ALT elevation > 20x ULN

Transaminase elevation	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 transaminases levels. While the investigator attributed the liver test abnormalities to alcoholic hepatitis rather than to study drug, the degree and pattern of transaminase elevation do not exclude an association between dalbavancin and transaminase elevations.

Another subject (subject ID 12001004) 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. 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 ALP 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 range. Repeat liver 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. Tests for viral hepatitides 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 status is unknown.

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

In conclusion, although none of the dalbavancin-treated subjects with liver tests abnormalities met Hy's law criteria, the degree of elevation and imbalance in liver 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 abnormalities in liver tests developed hepatocellular pattern of DILI although two subjects developed mixed injury, if categorized based on the R ratio as defined by modified definitions of the Council for International Organizations of Medical Sciences[3]. 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 $\geq$ 3x ULN and R $\geq$5
- Cholestatic: ALP $\geq$ 2x ULN and R$\leq$2
- Mixed: ALT $\geq$ 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 likely that dalbavancin may cause elevations of liver enzymes especially in patients with pre-existing liver dysfunction.

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 evaluated. 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 a case of muscle injury. Finally, transaminase elevations would be expected to be equally distributed between treatment arms.

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

8.6.2 Adverse Events Related to Hemorrhages

The safety databases for trials DUR001-301 and DUR001-302 were explored by conducting standardized MedDRA queries (SMQ). The SMQ identified a greater number of adverse events in the SMQ "Haemorrhages" in the dalbavancin arm. A total of 13 events in 12 (1.8%) subjects as compared to three events in three (0.5%) subjects were reported in the dalbavancin and comparator group, respectively. In all phase 2 and phase 3 dalbavancin trials, there were 36 (2%) versus 19 (1.5%) subjects included in the narrow SMQ "Haemorrhages" in the dalbavancin and comparator arms, respectively.

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

- Dalbavancin arm (13 events in 12 subjects): haemorrhagic anaemia (2), haematuria (2), gastrointestinal haemorrhage, melaena, haematochezia, upper gastrointestinal haemorrhage, petechiae, vessel puncture site haematoma, epistaxis, spontaneous haematoma, and wound haemorrhage.
- Comparator arm (3 events in 3 subjects): rectal haemorrhage, gastrointestinal haemorrhage, and epistaxis.

In prior phase 2 and 3 trials, there were 24 hemorrhage-related events in the dalbavancin group and 15 such events in the comparator group.

Coagulation tests were not a part of the laboratory investigations in the 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 two out of 12 subjects with hemorrhages received anticoagulants, namely enoxaparin. Whether this difference in AEs related to hemorrhages is attributed to chance, or indeed associated with dalbavancin is not certain. Nevertheless, the observed imbalance in these events between dalbavancin and comparator warrants closer attention to events of bleeding in the post-marketing period. It may be important, for instance, for patients undergoing surgery or taking anticoagulants.

8.7 Drug Class Associated Adverse Events and Other Adverse Events of Interest

8.7.1 Hypersensitivity Reactions

An anaphylactoid reaction that was considered study drug related and resulted in premature discontinuation of study drug was reported in the dalbavancin arm in trial DUR001-302. This was 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 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. The symptoms resolved within approximately 1 hour of initiation of treatment with dalbavancin. No information

Another subject in the dalbavancin arm was diagnosed with drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. This was a 71-year-old male with cellulitis with baseline temperature of 38.8°C and baseline transaminase and eosinophil elevation, **Table 34**. 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 1.2x 10^9/L from a baseline level of 0.8x 10^9/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 8.6x 10^9/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 34: Laboratory and Temperature Data in a Subject with Drug rash with eosinophilia and systemic symptoms

	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

The analysis of this case suggests that 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. Additionally 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. The search included 37 terms such as allergic edema, drug eruption, drug hypersensitivity, eosinophilia, rash etc. Conducted analyses did not demonstrate increased rates of hypersensitivity reactions in dalbavancin-treated subjects relative to comparator subjects. The number of subjects with preferred terms that may indicate allergic reactions was slightly higher in the comparator arm relative to the 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.

Of note, in trials DUR001-301 and DUR001-302, no dalbavancin-treated subject developed red man syndrome versus 2 comparator subjects. One subject in a thorough QT trial, developed red man syndrome while receiving an infusion of 1500 mg of dalbavancin.

8.7.2 Hematological Abnormalities

Because hematopoietic abnormalities are known to be associated with glycopeptides, this group of adverse events was specifically explored. A total of nine (1.3%) and six (0.9%) AEs related to decrease in white blood cell (WBC) counts and five (0.8%) and two (0.3%) events related to decrease in platelet counts were reported in the dalbavancin and comparator groups, respectively, in trials DUR001-301 and DUR001-302.

Subsequently the laboratory datasets for phase 2 and 3 dalbavancin trials were also searched for post-dose decreases in 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 35**.

Table 35: Subjects with Post-Baseline Decrease in WBC and Platelet Counts

	DUR001-301 and 302 trials		All phase 2 and 3 trials	
Subjects [a]	Dalbavancin N=652	Comparator N=651	Dalbavancin N=1778	Comparator N=1224
WBC < LLN	52 (8%)	49 (7.5%)	115 (6.5%)	91 (7.4%)
WBC ≤ 0.5x LLN	1 (0.15%)	0	2 (0.1%)	6 (0.5%)
Platelets < LLN	36 (5.5%)	41 (6.3%)	60 (3.4)	74 (6.0%)
Platelets ≤ 0.6 LLN	7 (1.1%)	4 (0.6%)	9 (0.5%)	8 (0.6%)

[a] Subjects with baseline blood cell counts greater than the lower limit of normal (LLN) and any post-baseline blood cell count less than LLN are included; subjects are counted once

8.7.3 Renal Toxicity

Because renal toxicity is a known to be associated with glycopeptides and the kidney was a target organ for toxicity in preclinical toxicology studies of dalbavancin, the adverse events related to renal impairment were explored, **Table 36**. The number of subjects with adverse events related to renal failure was low overall and the rates of renal impairment were similar in the dalbavancin and comparator arms.

Table 36: Adverse Events Related to Renal Toxicity

	DUR001-301 and 302 trials		All phase 2 and 3 trials	
	Dalbavancin N=652	Comparator N=651	Dalbavancin N=1778	Comparator N=1224
Total*	1 (0.15%)	4 (0.6%)	7 (0.4%)	12 (1%)
Renal failure	1 (0.15%)	1 (0.15%)	5 (0.3%)	4 (0.3%)
Renal failure acute	0	2 (0.3%)	1 (0.06%)	6 (0.5%)
Renal failure chronic	0	1 (0.15%)	0	1 (0.1%)
Renal function test abnormal	0	0	1 (0.06%)	0
Renal impairment	0	0	0	1 (0.1%)

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

An additional search for post-baseline creatinine elevation was also conducted, **Table 37**. 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 than or equal to 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 37: 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 (0.15%)	6 (0.9%)	4 (0.2%)	9 (0.7%)
Creatinine ≥ 2 Fold Increase from Baseline [b]	1 (0.15%)	7 (1.1%)	9 (0.5%)	12 (1%)

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

Conducted analyses do not indicate that dalbavancin is associated with increased rates of renal toxicities relative to comparators.

8.7.4 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 AE was specifically reviewed.

In trials DUR001-301 and DUR001-302, infusion site reactions occurred with similar frequencies in the dalbavancin and comparator arms. These reactions occurred in 12 (1.8%) dalbavancin and 14 (2.1%) comparator treated subjects in these trials. In all phase 2 and 3 trials, there were somewhat fewer infusion site reactions in the dalbavancin as compared to the comparator arm, 51 (2.9%) and 53 (4.3%), respectively.

8.7.5 Hyperglycemia and Hypoglycemia

The review of the initial submission of NDA 21883 found more subjects with hyperglycemia and hypoglycemia in the dalbavancin arms. Thus, in trials VER001-8 and -9 a total of 6 (0.6%) and 5 (0.5%) of 938 dalbavancin-treated subjects developed hyper- and hypoglycemia, respectively, as compared with 1 (0.3%) and 0 of 469 subjects with hyperglycemia 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 does not demonstrate the increase in glucose metabolism abnormalities in dalbavancin-treated subjects. 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 three times the upper limit of normal at any post-baseline measurement. In the new trials, hypoglycemia was observed in one (0.15%) dalbavancin-treated subject and in four (0.6%) vancomycin-treated subjects and hyperglycemia in 14 (2.1%) subjects in both treatment groups.

8.7.6 Ototoxicity

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 five subjects treated with dalbavancin and two 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.

Because audiologic studies or specific evaluations for ototoxicity were not conducted in the dalbavancin phase 2 and phase 3 clinical trials, the AEs potentially related to ototoxicity were evaluated. The only adverse event found by the broad SMQs "Hearing and vestibular disorders" and "Vestibular disorders" was dizziness reported by eight (1.2%) dalbavancin and six (1%) comparator treated subjects (ten and seven events, respectively). Otherwise, no AEs indicative of ototoxicity were reported.

9 POINTS FOR ADVISORY COMMITTEE DISCUSSION

1. Has the applicant provided substantial evidence of the safety and effectiveness of dalbavancin for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms?

    - If yes, please provide any recommendations concerning labeling.
    - If no, what additional studies/analyses are needed?