

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021883Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

### CLINICAL PHARMACOLOGY REVIEW

<b>NDA: 021-883</b>	Submission Date(s): 09/26/13
<b>Drug</b>	Dalbavancin
<b>Trade Name</b>	(N/A)
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<b>Sponsor</b>	Durata Therapeutics, Inc.
<b>Relevant IND(s)</b>	IND 60613
<b>Submission Type; Code</b>	Original New Drug Application (New Molecular Entity); Resubmission/After Withdrawal
<b>Formulation; Strength(s)</b>	Single-use, clear glass vials containing sterile powder equivalent to 500 mg of anhydrous dalbavancin
<b>Indication</b>	For the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms
<b>Dosage and Administration</b>	1000 mg IV on Day 1 and 500 mg IV on Day 8 infused over 30 min

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## Abbreviations

Ae, cumulative amount excreted in urine  
AUC, area under plasma concentration-time curve  
AUC<sub>0-24</sub>, area under plasma concentration-time curve over 24 hours  
AUC<sub>24</sub>: area under plasma concentration-time curve over 6 days divided by 6  
AUC<sub>avg</sub>, area under plasma concentration-time curve over 120 hours (5 days) divided by 5  
AUC<sub>inf</sub>, area under plasma concentration-time curve from time 0 to infinity  
C<sub>max</sub>, maximum observed plasma concentration  
CE, clinically evaluable analysis population  
CI, confidence interval  
CL, plasma clearance  
CL<sub>R</sub>, renal clearance  
CLSI, Clinical and Laboratory Standards Institute  
CrCL, creatinine clearance  
cSSSI, complicated skin and skin structure infections  
CV, coefficient of variation  
CYP450, cytochrome P450  
ESRD, end-stage renal disease  
*f*, free unbound (i.e., microbiologically active) drug  
HPLC, high performance liquid chromatography  
IRT, Interdisciplinary Review Team for QT Studies  
IV, intravenous  
LC-MS/MS, liquid chromatography with tandem mass spectrometry  
LLOQ, lower limit of quantification  
MIC, minimum inhibitory concentration  
MIC<sub>50</sub>, minimum inhibitory concentration for 50% of bacterial population  
MIC<sub>90</sub>, minimum inhibitory concentration for 90% of bacterial population  
MRSA, methicillin-resistant *Staphylococcus aureus*  
MSSA, methicillin-susceptible *Staphylococcus aureus*  
NDA, new drug application  
PD, pharmacodynamics  
PK, pharmacokinetics  
PK-PD, pharmacokinetics-pharmacodynamics  
QC, quality control  
QTcF, QT interval corrected according to Fridericia's method  
 $\Delta$ QTcF, change in QTcF from baseline  
 $\Delta\Delta$ QTcF, change in  $\Delta$ QTcF from placebo  
SAE, serious adverse event  
SD, standard deviation  
 $t_{1/2}$ , elimination half-life  
TEAEs, treatment-emergent adverse events  
T<sub>max</sub>, time of maximum observed plasma concentration  
TOC, test-of-cure visit  
V<sub>c</sub>, apparent volume of distribution of the central compartment  
V<sub>p1</sub>, apparent volume of distribution of the peripheral compartment 1  
V<sub>p2</sub>, apparent volume of distribution of the peripheral compartment 2

$V_{ss}$ , apparent steady-state volume of distribution

## 1 EXECUTIVE SUMMARY

The original New Drug Application (NDA) for dalbavancin was initially submitted for the treatment of complicated skin and skin structure infections by Vicuron Pharmaceuticals, Inc. on 12/21/2004. This original NDA was withdrawn by the Sponsor on 09/15/2008. On 09/26/2013, Durata Therapeutics, Inc. resubmitted the NDA to market the same drug product for acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms, including additional PK studies and Phase 3 studies. Dalbavancin is a lipoglycopeptide antibacterial drug and is active against susceptible Gram-positive microorganisms of *Staphylococcus aureus* (including methicillin-resistant strains [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, Group G Streptococci and viridans group streptococci. The proposed dosage regimen of dalbavancin in adults is 1000 mg IV on Day 1 and 500 mg IV on Day 8 infused over 30 min.

The majority of clinical studies were included in the original NDA submission, which were previously reviewed as follows:

- Eight Phase 1 studies to assess single and multiple dose pharmacokinetics, excretion and metabolism, penetration into skin blister fluid, and the impact of renal and hepatic impairment. The impact of demographics (age, gender, race, and weight) and concomitant medications on the pharmacokinetics of dalbavancin were assessed via population pharmacokinetic analysis.
- Two Phase 2 and three Phase 3 clinical studies to evaluate the safety and efficacy of dalbavancin for the treatment of catheter-related blood stream infections, uncomplicated skin and skin structure infections, and complicated skin and skin structure infections.

The Sponsor conducted two additional Phase 3 studies to support the approval of dalbavancin based on the modified FDA guidelines, as well as additional clinical pharmacology studies, summarized as follows and included in the current resubmission:

- Two new Phase 3 trials to evaluate safety and efficacy of dalbavancin for patients with ABSSSI (DUR001-301 and DUR001-302);
- One Phase 1 study to evaluate the PK and safety of supratherapeutic dose (single 1500 mg) of dalbavancin (DUR001-101).
- One thorough QT/QTc study to evaluate dalbavancin effect on the 12-lead ECG QTc interval in healthy subjects (DUR001-102).
- One PK study to assess safety and PK of dalbavancin in adolescent patients (12-16 years) (A8841004).

It should be noted that the Sponsor refers to an exposure-response (E-R) analysis using clinical response data from Study VER001-9 as a “PK-PD” analysis. Conventional terminology for target attainment analyses using nonclinical PK-PD targets is also referred to as “PK-PD” analyses. The remainder of this review will refer to the former (PK-PD rather than E-R) to be consistent with the Sponsor in order to reduce confusion.

## 1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed NDA 21-883, and it is acceptable from a clinical pharmacology perspective.

The reviewer concurs with the proposed dalbavancin dosage regimen of 1000 mg on Day 1 and 500 mg on Day 8. The dose should be adjusted to 750 mg on Day 1 and 375 mg on Day 8 for patients with severe renal impairment (creatinine clearance < 30 ml/min) and not receiving regular hemodialysis, as recommended by the sponsor.

The strategy of using clinical PK-PD relationships to inform determination of interpretive breakpoint criteria is an appropriate approach, but the clinical data included in the analysis was limited by a low number of failures and a narrow range on *S. aureus* MIC values across patients. The dalbavancin susceptibility breakpoint for *S. aureus* as proposed by the Sponsor is 0.25 mg/L. Based on FDA analysis of the PK-PD relationship for  $\geq 10\%$ , 20%, or 30% reduction in size of lesion area from baseline on Day 4, the clinical PK-PD analysis supports 0.06 mg/L as a susceptible breakpoint for *S. aureus*. Additionally, FDA nonclinical PK-PD target attainment analyses suggest a breakpoint of 0.125 mg/L is acceptable. Given these findings, the Sponsor's proposed breakpoint of 0.25 mg/L for *S. aureus* is not appropriate. The ultimate determination of the dalbavancin breakpoint will depend on the totality of information provided by each discipline and continues to be assessed at the time of the completion of this review.

## 1.2 Phase 4 Commitments

No Phase IV commitments are recommended.

## 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

### General PK Characteristics:

Dalbavancin mean C<sub>max</sub> and AUC increased nearly proportional to dose, following single and multiple dose intravenous (IV) administration in healthy subjects. The mean CL and VSS remained relatively constant across all doses and after multiple-dose administration. **Table 1.3-1** presents dalbavancin pharmacokinetic 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 1.3-1**. In patients with infections, the mean CL and central volume of distribution (V<sub>c</sub>) were 43% and 28% higher than those in healthy subjects, respectively.

**Table 1.3-1. Dalbavancin Pharmacokinetic Parameters in Healthy Subjects**

Parameter	Single 1000 mg Dose
$C_{max}$ (mg/L)	287 (13.9) <sup>1</sup>
AUC <sub>0-24</sub> (mg•h/L)	3185 (12.8) <sup>1</sup>
AUC <sub>0-Day7</sub> (mg•h/L)	11160 (41.1) <sup>2</sup>
AUC <sub>0-∞</sub> (mg•h/L)	23443 (40.9) <sup>2</sup>
Terminal $t_{1/2}$ (h)	346 (16.5) <sup>2,3</sup>
CL (L/h)	0.0513 (46.8) <sup>2</sup>

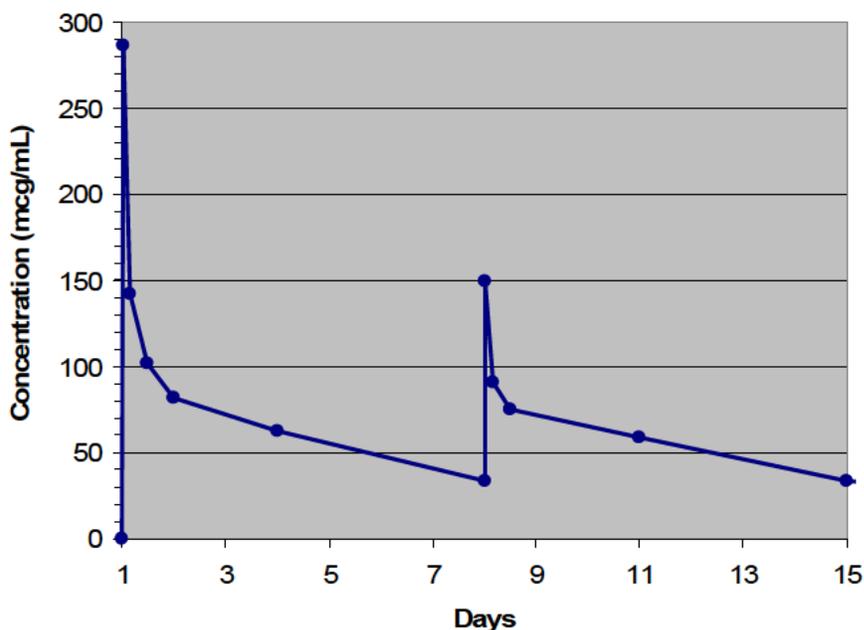
All values are presented as mean (% coefficient of variation)

<sup>1</sup> Data from 50 healthy subjects.

<sup>2</sup> Data from 12 healthy subjects.

<sup>3</sup> 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 1.3-1.** 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<sub>0-7days</sub> (blister fluid)/AUC<sub>0-7days</sub> (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, 20% of the dose was excreted in feces through 70 days postdose. Approximately 19-33% of the administered dose was excreted as unchanged dalbavancin and 8-12% of the dose as OH-dalbavancin after 42 to 68 days, which was approximately 27-45% of the administered dose excreted in urine.

### **Intrinsic Factors:**

#### ***Body Surface Area (BSA)***

BSA was identified as an influential covariate on CL in the PopPK analysis. These results indicated that a positive relationship between CL and BSA was observed and the variation of individual CL from 79.1% to 161% of population mean was associated with BSA ranging from 1.3 to 3.85 m<sup>2</sup> in ABSSSI patients from a Phase 3 study. However, limited clinical relevance of these covariate impacts was expected, as clinical success rate was high (over 85%). No dose adjustment was recommended based on BSA.

#### ***Elderly/Gender/Race***

The impact of covariates such as age, gender, and race on the pharmacokinetics of dalbavancin were evaluated with the population pharmacokinetic 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 pharmacokinetics of dalbavancin were evaluated in hospitalized adolescents (12-16 years of age) receiving antibiotic therapy, following a single 30-min IV infusion of dalbavancin 1000 mg for those with body weight  $\geq$ 60 kg or 15 mg/kg for <60 kg. Dalbavancin C<sub>max</sub> and AUC<sub>inf</sub> were comparable following these doses in adolescent patients. The mean C<sub>max</sub> 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 Sponsor did not intend to propose a dose adjustment for adolescents based on these results, nor did the sponsor seek approval for treatment of ABSSSI in adolescents.

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

### ***Renal impairment***

The impact of mild, moderate, and severe renal impairment as well as end-stage renal disease (ESRD) on the pharmacokinetics of dalbavancin was assessed in three clinical studies. Mean CL was 11% and 35% lower and mean AUC<sub>inf</sub> 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<sub>inf</sub> 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<sub>inf</sub> 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 pharmacokinetics of dalbavancin were 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 C<sub>max</sub> and AUC<sub>inf</sub> were similar in subjects with mild hepatic impairment compared to control subjects. However, mean C<sub>max</sub> (day 1) and AUC<sub>inf</sub> 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.

### **Extrinsic Factors:**

#### ***Drug-Drug Interactions***

Based on the findings from in vitro metabolism and transporter studies that dalbavancin is neither an inhibitor nor a substrate of CYP450 isoenzymes or P-gp efflux transporter, no clinical drug-drug interaction studies were conducted.

### **Population PK (PopPK) Analysis:**

A total of 1668 dalbavancin concentrations from 532 subjects from three Phase 2/3 studies were included in the PopPK analysis. The more recent Phase 3 studies (DUR001-301 and 302) were not included in the PopPK analysis, since dalbavancin concentration in plasma was not measured

in these studies. 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 of total clearance (CL) was 0.046 L/hr and the population mean of V<sub>ss</sub> 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 (V<sub>c</sub>) and peripheral compartments (V<sub>p1</sub>) and CRCL included on CL. Albumin, sex, and age were also important covariates but not considered to be as significant as BSA and CRCL.

### **Exposure-Response for Efficacy:**

#### ***Animal Models of Infection***

The unbound AUC<sub>0-24</sub> 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.

#### ***Exposure-Response Analyses***

### **Exposure-Response for Efficacy:**

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

- AUC<sub>avg</sub>/MIC of equal or greater than 13,658, 14,472, and 21,267 was associated with a higher percentage of patients achieving microbiological success at End of Therapy (EOT), clinical success at Test of Cure (TOC), or microbiological success at TOC (>90.9%, 98.4%, or 92.6%, respectively).
- AUC<sub>avg</sub>/MIC of equal or greater than 16,096, 13,396, or 14,320 was significantly associated with a higher percentage of patients achieving ≥ 10, 20, or 30% reduction from baseline in the area of infection on Day 4 (91.3%, 86.3%, or 81.3%, respectively).

The PK-PD relationship between AUC<sub>avg</sub>/MIC and clinical response at TOC or reduction in lesion size on Day 4 was used to inform establishing in vitro interpretive criteria for dalbavancin against *S. aureus*. The Sponsor proposed a susceptibility interpretive criterion (breakpoint) of ≤ 0.25 mg/L based on the model-predicted probability of achieving Clinical success at TOC, as presented in **Table 1.3-2**. However, FDA analysis demonstrated that the number of *S. aureus* isolates from the Phase 3 clinical trial with MIC values of 0.25 mg/L was less than 0.2% while over 96% isolates had MICs of ≤ 0.06 mg/L. The PK-PD relationship for ≥ 10% or 20% reduction from baseline in the area of infection on Day 4 demonstrated a dalbavancin breakpoint of 0.06 mg/L for *S. aureus* is more appropriate given the limitations of the data. Additionally, FDA nonclinical PK-PD target attainment analyses suggest a breakpoint of 0.125 mg/L is acceptable. Collectively, these FDA analyses indicate the Sponsor's proposed breakpoint of 0.25 mg/L for *S. aureus* is not appropriate.

**Table 1.3-2.** Mean model-predicted percent probabilities of response by MIC value for dalbavancin against *S. aureus*.

MIC	Mean model-predicted probability of responses				
	Clinical success at TOC	Microbiological success at EOT	≥ 10% reduction from baseline in the area of infection on Day 4	≥ 20% reduction from baseline in the area of infection on Day 4	≥ 30% reduction from baseline in the area of infection on Day 4
0.03	100	90.8	90.5	85.4	79.6
0.06	96.7	90.1	89.6	84.6	78.6
0.12	89.2	70.3	77.5	61.4	48.4
0.25	89.1	64.3	75.8	53.8	38.5

**Exposure-Response for Safety:**

In the current dalbavancin NDA resubmission, no exposure-response analysis was performed for safety since assessments of drug exposure were not performed and only one dose regimen for dalbavancin was studied in the two new Phase 3 studies supporting the ABSSSI indication.

**Cardiovascular effects**

A thorough QT study was conducted in healthy adults with a single supratherapeutic dose of IV dalbavancin (1500 mg). A small, concentration-dependent effect of dalbavancin on the placebo-corrected, change-from-baseline in QTcF ( $\Delta\Delta\text{QTcF}$ ) was identified with an estimated slight negative population slope of -0.0051 msec/ $\mu\text{g}/\text{mL}$  and a zero intercept. For a complete assessment of the thorough QT study findings, refer to the Interdisciplinary Review Team review.

## 2 QUESTION-BASED REVIEW

The majority of clinical studies for dalbavancin have been reviewed during the original NDA submission review cycle. Details regarding clinical pharmacology information of dalbavancin submitted during the original NDA submission review cycle can be found in the previous clinical pharmacology review by Dr. Charles R Bonapace dated 09/20/2005. The current dalbavancin NDA resubmission includes three new PK studies and two new Phase 3 studies. This QBR review focuses on these PK studies and an assessment of the population PK and PK-PD analyses included in the current submission. Only relevant sections of the QBR are addressed.

### 2.1 General Attributes of the Drug

For highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology, please refer to the previous clinical pharmacology review dated 09/20/2005.

#### 2.1.1 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Like other glycopeptides, dalbavancin interferes with cell wall formation by binding to the terminal D-alanyl- D-alanine (D-ala-D-ala) of the stem peptide in nascent peptidoglycan, inhibiting cross-linking. This appears to be the only relevant action that dalbavancin exerts on bacteria.

The proposed therapeutic indication of dalbavancin is acute bacterial skin and skin structure infections (ABSSSI) caused by *Staphylococcus aureus* including methicillin-resistant and multidrug-resistant (MDR) strains, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, Group G streptococci, and viridans group streptococci.

#### 2.1.2 *What are the proposed dosage(s) and route(s) of administration?*

The proposed dosage regimen of dalbavancin for adults is 1000 mg on day 1 and 500 mg on day 8 for the treatment of acute bacterial skin and skin structure infections administered as an intravenous infusion over 30 min.

### 2.2 General Clinical Pharmacology

#### 2.2.1 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

The proposed dalbavancin dosing regimen of 1000 mg IV on Day 1 and 500 mg IV on Day 8 was considered acceptable from a clinical pharmacology standpoint in the original review cycle. After the withdrawal in 2008, the Sponsor conducted five Phase 1 studies to assess dalbavancin PK in adolescents (12-17 years), effect on QT prolongation following therapeutic and suprathreshold doses, PK in Japanese, and long term exposure following multiple doses. Two additional Phase 3 studies (DUR001-301 and DUR001-302) were completed evaluating the

efficacy and safety of dalbavancin for the treatment of patients with a suspected or proven gram-positive ABSSSI. **Table 2.2.1-1** summarizes these clinical trials used to support dalbavancin dosing.

**Table 2.2.1-1** Phase 1 and Phase 3 clinical trials used to support dalbavancin dosing.

Study #	Purpose	Dalbavancin regimen	Endpoint
A8841004 (Phase 1)	PK Adolescents (12-16 yrs)	1000 mg single for $\geq 60$ kg or 15 mg/kg single for $< 60$ kg	n/a
DUR001-101 (Phase 1)	PK following a suprathreshold dose	1500 mg single	n/a
DUR001-102 (Phase 1)	Effect on QT prolongation	1000 mg or 1500 mg single	n/a
DUR001-301(Phase 3)	Efficacy and safety for treatment of ABSSSI	1000 mg on Day 1, then 500 mg on Day 8	Early clinical response at Day 4 or Day 8
DUR001-302 (Phase 3)	Efficacy and safety for treatment of ABSSSI	1000 mg on Day 1, then 500 mg on Day 8	Early clinical response at Day 4 or Day 8

*2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?*

In the original dalbavancin NDA submission, the primary efficacy endpoint in the Phase 3 studies (VER001-8, VER001-9, and VER001-16) was the clinical response at the test-of-cure (TOC) visit in the clinically evaluable population, and the secondary efficacy endpoints consisted of the clinical response, microbiological response, and overall response for the intent-to-treat (ITT), micro ITT, clinically evaluable, and microbiologically evaluable populations.

According to the recent FDA Guidance for Industry “Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment”, the two new Phase 3 studies (DUR001-301 and DUR001-302) used early clinical response after 48 to 72 hours of therapy as the primary efficacy endpoint for the treatment of patients with a suspected or proven Gram-positive ABSSSI. The secondary efficacy endpoints included clinical response at the end-of-treatment visit (EOT), at the short-term follow-up visit (SFU) and the long-term follow-up visit (LFU), and microbiological response in ITT, micro ITT, clinically evaluable, and microbiologically evaluable populations.

In both Phase 3 studies, clinical efficacy outcome was assessed based on measurements of lesion size for infection site assessment and temperature as a physical sign of systemic inflammation. For primary efficacy endpoints, clinical responder was defined as no increase in lesion area and resolution of fever after the first dose. For the secondary endpoints, clinical success was defined as decrease in lesion area and resolution of local and systemic symptoms at the EOT visit (study day 14-15). Microbiologic success is defined as eradication or presumed eradication whereas a failure is defined as persistence or presumed persistence.

*2.2.3 Exposure-Response*

*2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.*

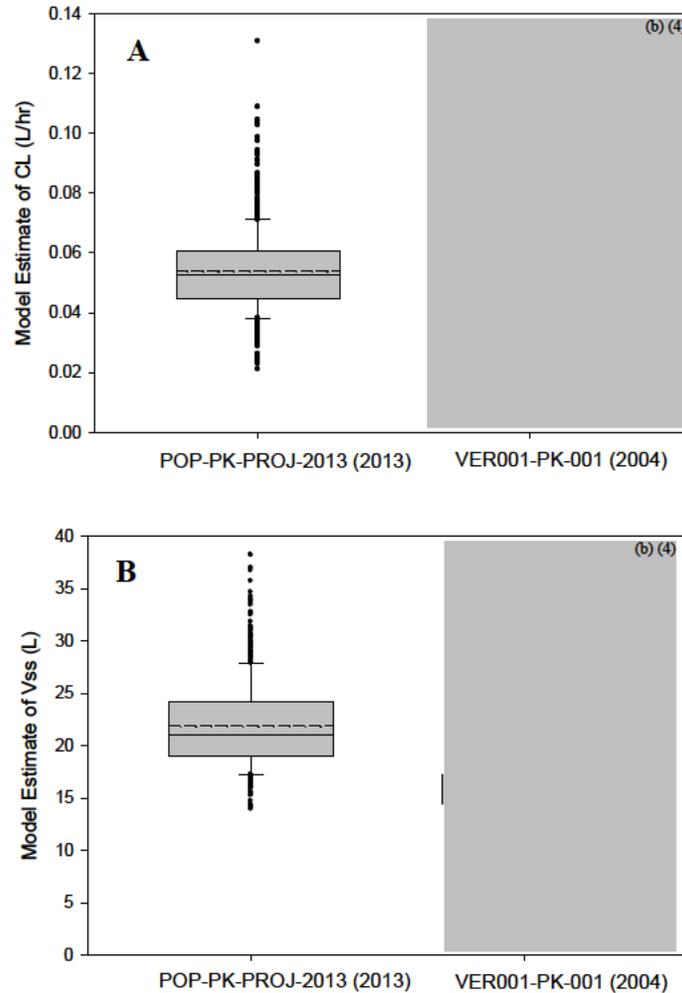
The following review questions were identified and addressed based on the sponsor's pharmacometric/exposure-response analyses included in the current submission.

*2.2.3.1.1 Are the major dalbavancin PK parameter estimates in agreement between the previously submitted modeling analysis and the present reanalysis?*

In the original dalbavancin NDA submission, a population PK (PopPK) analysis was included (VER001-PK-001, 06/10/2004). The final PK dataset consisted of a total of 1668 dalbavancin concentrations from 532 subjects in three Phase 2/3 studies (Studies VER001-4, VER001-5, and VER001-9) (b) (4)

In the current NDA resubmission, assessments of drug exposure were not performed in the two new Phase 3 studies supporting the ABSSSI indication. Thus, the same dalbavancin PK data included in the Sponsor's original NDA submission were re-analyzed in the newly submitted and updated population analysis performed by another CRO company (POP-PK-PROJ-2013). The plasma concentration-time profiles of dalbavancin were described using a three-compartment model with a zero order input and a first order elimination. **Figure 2.2.3.1.1-1** presents comparison of CL and Vss from the two versions of PopPK models. (b) (4)

**Figure 2.2.3.1.1-1.** Comparison of the parameter estimates of CL (Panel A) and Vss (Panel B) from the two PopPK analyses. The boxplots (solid lines) represent 10<sup>th</sup>, 25<sup>th</sup>, median, 75<sup>th</sup>, and 90<sup>th</sup> percentiles of the estimates. The dash lines are the mean values of PK parameter estimates.



The major PK parameters from both PopPK models, such as CL and Vss, were further compared at individual levels, as shown in **Figure 2.2.3.1.1-2.** (b) (4)

(b) (4). Please consult the pharmacometrics review for more information on dalbavancin PK in patients (see Appendix 4.2. Pharmacometrics review).

**Figure 2.2.3.1.1-2.** Consistency of CL (Panel A) or V<sub>ss</sub> (Panel B) from each subject between the two versions of PopPK models.



*2.2.3.1.2 Are the in vitro susceptibility test interpretive criteria for dalbavancin appropriately determined? If not, what susceptibility breakpoint is recommended?*

The Sponsor proposed a susceptibility breakpoint for dalbavancin for *S. aureus* of  $\leq 0.25$  mg/L and that the more recent re-evaluation of preclinical and clinical data supported this breakpoint value. Pharmacokinetic-pharmacodynamic (PK-PD) analyses to support this proposal were conducted using individual predicted exposures and efficacy endpoints from Study VER001-9 in order to identify threshold  $AUC_{avg}/MIC$  values associated with clinical response.

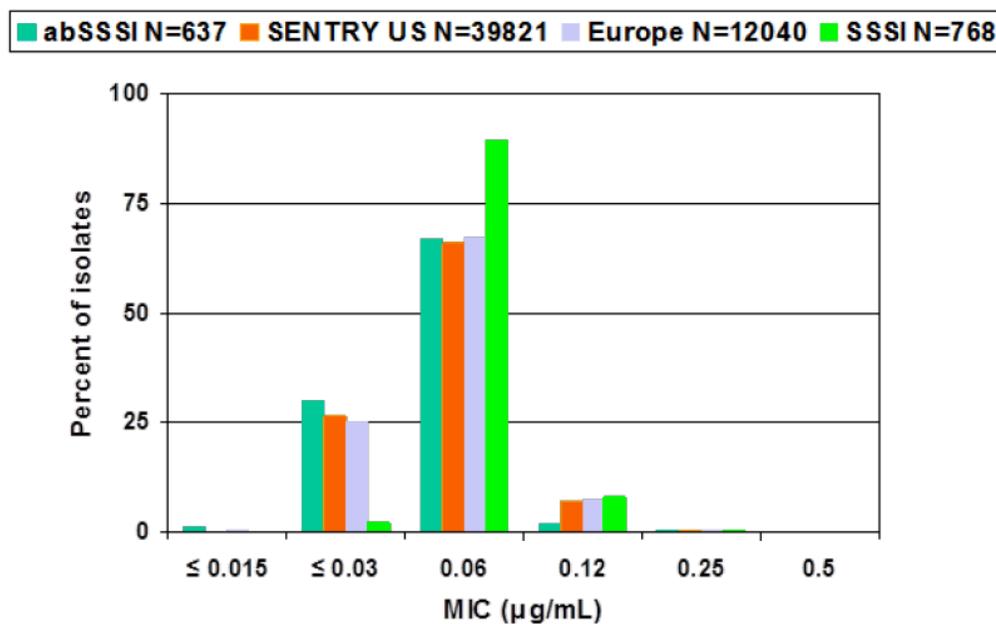
However, the proposed susceptibility breakpoint of  $\leq 0.25$  mg/L is considered inappropriate, based on the reviewer's assessment for dalbavancin MIC distributions in clinical trials and surveillance programs, target attainment with animal data, and a reanalysis of PK-PD

relationships with clinical efficacy data. These assessments support dalbavancin susceptibility breakpoint either 0.06 or 0.125 mg/L.

***Dalbavancin MIC distributions in clinical trials and surveillance programs***

A MIC frequency distribution was previously constructed using dalbavancin MIC values from dalbavancin clinical efficacy studies and a number of surveillance studies. **Figure 2.2.3.1.2-1**, provided by the Sponsor, depicts the dalbavancin MIC distributions for the baseline isolates from the ABSSSI trials and more recent U.S. (SENTRY 2002-2012) and European (SENTRY 2006-2009; 2011-2012) surveillance data. The MIC distribution is very similar in clinical trials and surveillance studies. Dalbavancin MICs remain clustered at 0.03 and 0.06 mg/L, with few isolates at 0.25 and 0.5 mg/L. These data suggest that the susceptibility breakpoint should be either 0.06 or 0.125 mg/L, which is at least one dilution factor lower than the Sponsor’s proposed breakpoint of 0.25 mg/L.

**Figure 2.2.3.1.2-1.** Dalbavancin MIC Distributions: *S. aureus* Isolates from Clinical Trials (ABSSSI and Complicated and Uncomplicated SSSI Baseline Isolates) and Surveillance Studies



***Probability of Target Attainment Using Animal Data (Sponsor’s analysis in previous review cycle, 2005)***



Several caveats were recognized by the reviewer regarding using a target attainment approach using targets identified in animal models for susceptibility breakpoint determination, as follows:

- a. The target for relevant PK-PD parameters (AUC/MIC, C<sub>max</sub>/MIC, or % T>MIC) determined in an animal infection model may differ from the desired target threshold associated with clinical response. Targets identified from animal models should be well justified in order to be reasonably applied for predicting probability of target attainment in clinical studies.
- b. Variability of drug exposure in humans may differ from that in animals. This difference in variability may translate into a target that is not applicable to calculating probability of target attainment in humans.

Therefore, the reviewer recommends that the previously proposed dalbavancin breakpoint obtained by using nonclinical target attainment methods should be carefully interpreted by merging with clinical relevant evidence for the ultimate determination of breakpoint.

***PK-PD Relationships for Establishing Dalbavancin Susceptibility Breakpoint***

In the current NDA submission, the Sponsor used dalbavancin exposure and the associated clinical efficacy data in a Phase 3 study in patients with ABSSSI (VER001-9) to establish the dalbavancin susceptibility break point. The PK-PD relationships were first developed between  $AUC_{avg}/MIC$  and efficacy endpoints on Day 4, TOC, or EOT, as shown in **Table 2.2.3.1.2-1**. These univariable analyses demonstrated that 1)  $AUC_{avg}/MIC$  of equal or greater than 13,658, 14,472, and 21,267 was associated with a higher percentage of patients achieving microbiological success at End of Therapy (EOT), clinical success at Test of Cure (TOC), or microbiological success at TOC (>90.9%, 98.4%, or 92.6%, respectively); and 2)  $AUC_{avg}/MIC$  of equal or greater than 16,096, 13,396, or 14,320 was significantly associated with a higher percentage of patients achieving  $\geq 10$ , 20, or 30% reduction from baseline in the area of infection on Day 4 (91.3%, 86.3%, or 81.3%, respectively).

**Table 2.2.3.1.2-1.** Summary of univariable relationships between dichotomous efficacy endpoints and  $AUC_{avg}/MIC$

Efficacy endpoint	All patients				Patients with <i>S. aureus</i>			
	$AUC_{avg}/MIC$ ratio threshold	Patients < or $\geq$ threshold achieving efficacy endpoint		P-value	$AUC_{avg}/MIC$ ratio threshold	Patients < or $\geq$ threshold achieving efficacy endpoint		P-value
		< threshold % (n/N)	$\geq$ threshold % (n/N)			< threshold % (n/N)	$\geq$ threshold % (n/N)	
Clinical success at EOT	16,038	90.6 (29/32)	96.6 (144/149)	0.15	21,267	93.9 (107/114)	100 (53/53)	0.10
Microbiological success at EOT	14,472	66.7 (10/15)	90.9 (150/165)	0.015	14,472	64.3 (9/14)	90.8 (138/152)	0.012
Clinical success at TOC	21,267	89.3 (100/112)	98.4 (62/63)	0.034	21,267	89.1 (98/110)	100 (52/52)	0.01
Microbiological success at TOC	13,658	75.0 (9/12)	92.6 (151/163)	0.07	13,658	75.0 (9/12)	92.7 (139/150)	0.07
$\geq 10\%$ reduction from baseline in the area of infection on Day 4	16,096	77.1 (27/35)	91.3 (137/150)	0.033	16,096	75.8 (25/33)	90.5 (124/137)	0.035
$\geq 20\%$ reduction from baseline in the area of infection on Day 4	13,396	50.0 (5/10)	86.3 (151/175)	0.01	14,320	53.8 (7/13)	85.4 (134/157)	0.011
$\geq 30\%$ reduction from baseline in the area of infection on Day 4	14,320	42.9 (6/14)	81.3 (139/171)	0.003	14,320	38.5 (5/13)	79.6 (125/157)	0.003

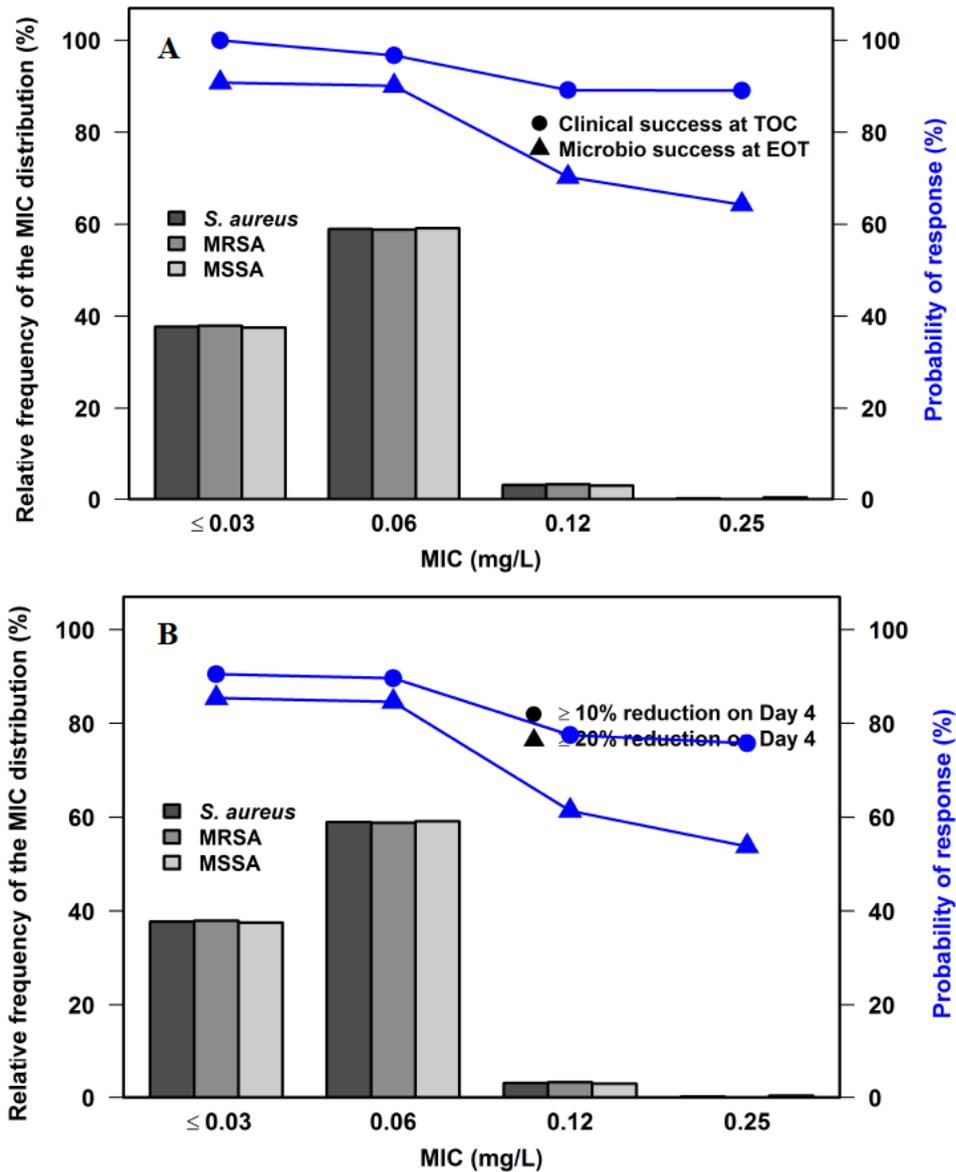
By using the results of PK-PD analyses for efficacy and Monte Carlo simulation, the probability of achieving clinical efficacy endpoints at each MIC category was predicted, as shown in **Table 2.2.3.1.2-2**. (See Appendix 4.2 Pharmacometrics review for details.)

**Table 2.2.3.1.2-2.** Mean Predicted Probabilities of Response by MICs for Dalbavancin against *S. aureus*.

MIC (mg/L)	Mean model-predicted probability of responses				
	Clinical success at TOC	Microbiological success at EOT	≥ 10% reduction from baseline in the area of infection on Day 4	≥ 20% reduction from baseline in the area of infection on Day 4	≥ 30% reduction from baseline in the area of infection on Day 4
0.03	100	90.8	90.5	85.4	79.6
0.06	96.7	90.1	89.6	84.6	78.6
0.12	89.2	70.3	77.5	61.4	48.4
0.25	89.1	64.3	75.8	53.8	38.5

The Sponsor proposed a susceptibility break point of  $\leq 0.25$  mg/L for dalbavancin against *S. aureus*, based on the predicted probability of achieving Clinical success at TOC. However, the number of failures in the Phase 3 study were limited and the number of *S. aureus* isolates with MIC values of 0.25 mg/L was less than 0.2% while over 96% isolates had MICs of  $\leq 0.06$  mg/L. The reviewer’s analysis revealed that a susceptibility break point of 0.06 mg/L is more appropriate based on the predicted probability of achieving  $\geq 10\%$  or  $20\%$  reduction in the size of lesion area on Day 4. This considers more significant PK-PD relationships for efficacy endpoints on Day 4 and the majority of occurrences of isolates with 0.06 mg/L MIC in the all Phase 3 studies. **Figure 2.2.3.1.2-3** depicts the predicted probabilities of efficacy endpoints overlaid with the MIC distribution for *S. aureus*. (See Appendix 4.2 Pharmacometrics review for details of the analysis). This result supports a dalbavancin breakpoint of 0.06 mg/L for *S. aureus*.

**Figure 2.2.3.1.2-3.** Probabilities of efficacy endpoints overlaid with the MIC distribution for *S. aureus* and the subsets of MRSA and MSSA isolates, including Clinical success at TOC and Microbiological success at EOT (Panel A), 10% and 20% reduction in size of lesion area on Day 4 (Panel B).



***Probability of Target Attainment Using Animal Data (Reviewer’s analysis, current review cycle, 2013)***

As indicated in the nonclinical study (VER001-MI-013), free AUC<sub>24</sub>/MIC was demonstrated as the best predictive PK-PD parameter for drug efficacy in murine neutropenic thigh infection model. The AUC<sub>24</sub> was defined by AUC from 0 to 6 days divided by 6, which is similar to the definition of AUC<sub>avg</sub> (AUC<sub>0-120hr</sub>/5) used in the Sponsor’s PK-PD analysis. The targets of free drug AUC<sub>24</sub>/MIC associated with a static, 1-log kill, or 2-log kill effect were 265, 268, or 332 for *S. aureus*, respectively. In this analysis, the same 5000 hypothetical patients generated by

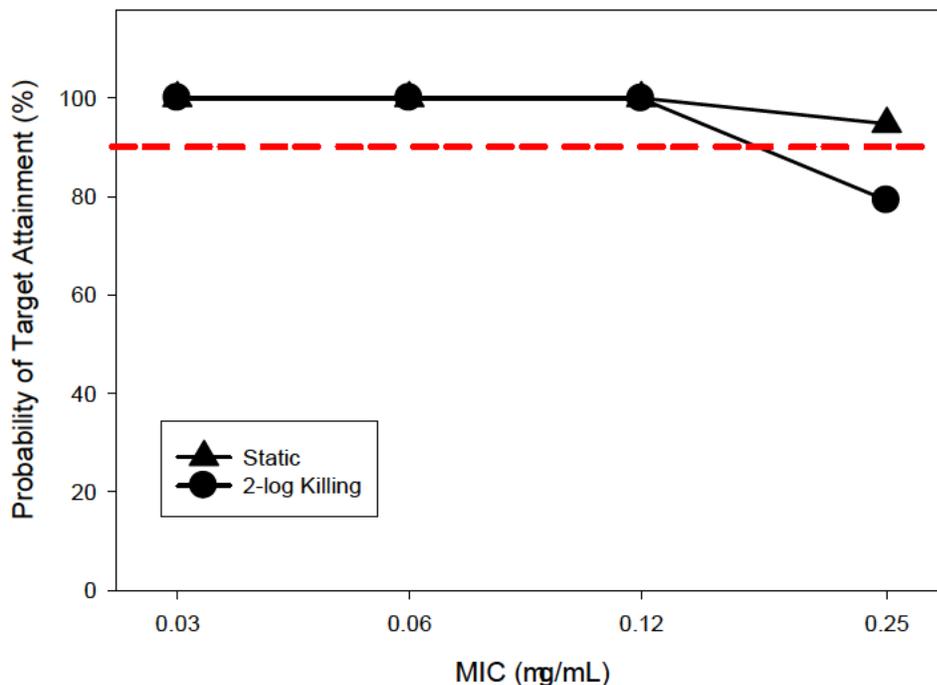
Monte Carlo simulations in the Sponsor's PK-PD analysis (ICPD-00280) were included. Taking free drug fraction of 7% in human plasma, free  $AUC_{avg}/MIC$  was obtained for each MIC. Percentages of patients achieving the static or 2-log kill target were calculated in the simulated population, as shown in **Table 2.2.3.1.2-3**. **Figure 2.2.3.1.2-4** depicts the probability of achieving these targets at each MIC. These nonclinical target attainment results support a dalbavancin breakpoint of 0.12 to 0.25 mg/L for *S. aureus*.

**Table 2.2.3.1.2-3** Probability of patients achieving the static or 2-log kill target in the simulated population.

Free AUC24/MIC Target <sup>a</sup>	MIC			
	0.03	0.06	0.12	0.25
Static	100	100	100	94.8
2-log Kill	100	100	99.9	79.2

<sup>a</sup>  $AUC_{avg}/MIC$  and  $AUC_{24}/MIC$  are similar. So, the free  $AUC_{24}/MIC$  was used for calculation of probability.

**Figure 2.2.3.1.2-4.** Probabilities of Simulated Target Attainment (Dalbavancin free  $AUC_{avg}/MIC$ ) for *S. aureus*. Triangles represent the static target and circles represent the 2-log killing target. The red dash line is 90% probability.



**Overall Summary of Dalbavancin Breakpoint Determination by the Sponsor and FDA**

Different approaches were employed by the Sponsor and FDA reviewer for determination of a *S. aureus* susceptibility breakpoint for dalbavancin. Data from VER001-9 were used for identifying clinical PK-PD relationships in the Sponsor and the reviewer's analyses. In addition, the review considered MIC distributions in clinical trials and surveillance programs and nonclinical target

attainment data. **Table 2.2.3.1.2-4** summarizes dalbavancin breakpoints proposed by the Sponsor and recommended by FDA.

**Table 2.2.3.1.2-4** Comparison of breakpoints from the Sponsor and FDA

Determination Method	Sponsor		FDA	
	Nonclinical PK-PD (Target Attainment, 2005)	Clinical PK-PD (2013)	Nonclinical PK-PD (Target Attainment, 2013)	Clinical PK-PD (2013)
Target of AUC/MIC from Animal Study	(b) (4)	n/a	fAUC24/MIC: Static: 265 2-log kill:332	n/a
Efficacy Endpoint		Clinical success at TOC	n/a	≥ 20% reduction in area of infection on Day 4
Dalbavancin Breakpoint mg/L)		0.25	0.12-0.25	0.06

AUC24: AUC from 0 to 6 days divided by 6

The FDA guidance recommends using early clinical response as primary efficacy endpoint. Thus the clinical response data from clinical response on Day 4 (rather than TOC) may be considered more informative for determination of a dalbavancin breakpoint for *S. aureus*. Therefore, the proposed susceptibility breakpoint of  $\leq 0.25$  mg/L by the Sponsor is not appropriate, and a lower dalbavancin breakpoint of 0.06 mg/L for *S. aureus* would be suggested based on the rationale above. This is further supported by dalbavancin MIC data from clinical trials and surveillance clustered at 0.03 and 0.06 mg/L, with few isolates at 0.25 and 0.5 mg/L. These data suggest that the susceptibility breakpoint should be either 0.06 or 0.125 mg/L, which is at least one dilution factor lower than the Sponsor's proposed breakpoint of 0.25 mg/L. A breakpoint of 0.06 or 0.125 mg/L is also supported by the reviewer's nonclinical PK-PD target attainment analysis using the PopPK model and ABSSSI patients in Study VER001-9. In summary, the Sponsor's proposed susceptibility breakpoint of  $\leq 0.25$  mg/L for dalbavancin for *S. aureus* is not acceptable; a breakpoint of either 0.06 or 0.125 mg/L is more appropriate given the data analyzed.

It should be also noted that the determination of breakpoints involves multiple disciplines including clinical and microbiological perspectives in addition to the above nonclinical and clinical PK-PD observations of the clinical pharmacology reviewer. The ultimate determination of the dalbavancin breakpoint will depend on the totality of information provided by each discipline and continues to be assessed at the time of the completion of this review.

*2.2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.*

The target organ toxicities and the adverse events of dalbavancin in the Phase 2 and 3 clinical trials were previously reviewed in the original NDA submission. Please refer to the clinical pharmacology review dated 09/20/2005 for details. The current submission includes two new Phase 3 clinical trials with dalbavancin and comparators. This section focuses on overall safety assessment in the dalbavancin clinical development programs, including concerns related to impact of dalbavancin on hepatobiliary function in the new Phase 3 trials.

**Table 2.2.3.2-1** summarizes treatment-emergent adverse events (TEAEs) during the clinical development program of dalbavancin. The overall proportions of subjects experiencing TEAEs and treatment-related TEAEs were higher in the dalbavancin group in the Phase 1 integrated analysis set relative to the comparator group. The overall proportion of subjects experiencing TEAEs and treatment-related TEAEs was lower in the Phase 2/3 integrated analysis set for subjects treated with dalbavancin relative to subjects treated with comparator. The overall incidences of subjects experiencing deaths, SAEs, and premature discontinuation of study drug due to TEAEs, and study withdrawals due to TEAEs were low, similar between dalbavancin and comparator groups, and similar amongst the Phase 1, Phase 2/3, and Phase 3 (DUR001-301/302) integrated analysis sets.

**Table 2.2.3.2-1. Overview of Treatment-Emergent Adverse Events: Safety Population**

Number (%) of Subjects with:	Phase 1 Integrated Analysis Set		Phase 2/3 Integrated Analysis Set		Phase 3 DUR001-301/302 Integrated Analysis Set	
	Dalbavancin (N=286)	Comparator (N=122)	Dalbavancin (N=1778)	Comparator (N=1224)	Dalbavancin (N=652)	Comparator (N=651)
Any TEAE <i>P</i> value <sup>a</sup>	180 (62.9)	36 (29.5)	799 (44.9)	573 (46.8)	214 (32.8)	247 (37.9)
Any Tx-related TEAE <i>P</i> value <sup>a</sup>	99 (34.6)	21 (17.2)	328 (18.4)	246 (20.1)	80 (12.3)	89 (13.7)
Any SAE <i>P</i> value <sup>a</sup>	4 (1.4)	0	109 (6.1)	80 (6.5)	17 (2.6)	26 (4.0)
Any Tx-related SAE <i>P</i> value <sup>a</sup>	0	0	3 (0.2)	9 (0.7)	2 (0.3)	4 (0.6)
Discontinuations from Study Drug Due to TEAE <i>P</i> value <sup>a</sup>	4 (1.4)	1 (0.8)	53 (3.0)	35 (2.9)	14 (2.1)	13 (2.0)
Withdrawals from Study Due to TEAE <i>P</i> value <sup>a</sup>	0	0	17 (1.0)	6 (0.5)	0	0
Deaths <i>P</i> value <sup>a</sup>	0	0	10 (0.6)	14 (1.1)	1 (0.2)	7 (1.1)

Source: Module 5, ISS, Table 4.1-1, Table 4.1-2.1.1, and Table 4.1-2.1.2

<sup>a</sup> *P*-value is for Dalbavancin vs. Comparator and is from the Cochran-Mantel-Haenszel test of general association, stratified by study. *P* values were not calculated for the phase 1 integrated analysis set.

Note: Treatment-related AEs are defined as those reported as possibly or probably related to study treatment or AEs for which the relationship was missing. Adverse events with missing intensity are considered severe. For summarizations of number of subjects, subjects are only counted once; for number of AE summarizations, subjects may be counted multiple times, according to the number of AEs experienced. Percentages of total number of treatment-related AEs and SAEs are based on total number of AEs.

Abbreviations: ISS = Integrated Summary of Safety; SAE = serious adverse event; TEAE = treatment-emergent adverse event.  
Tx=treatment

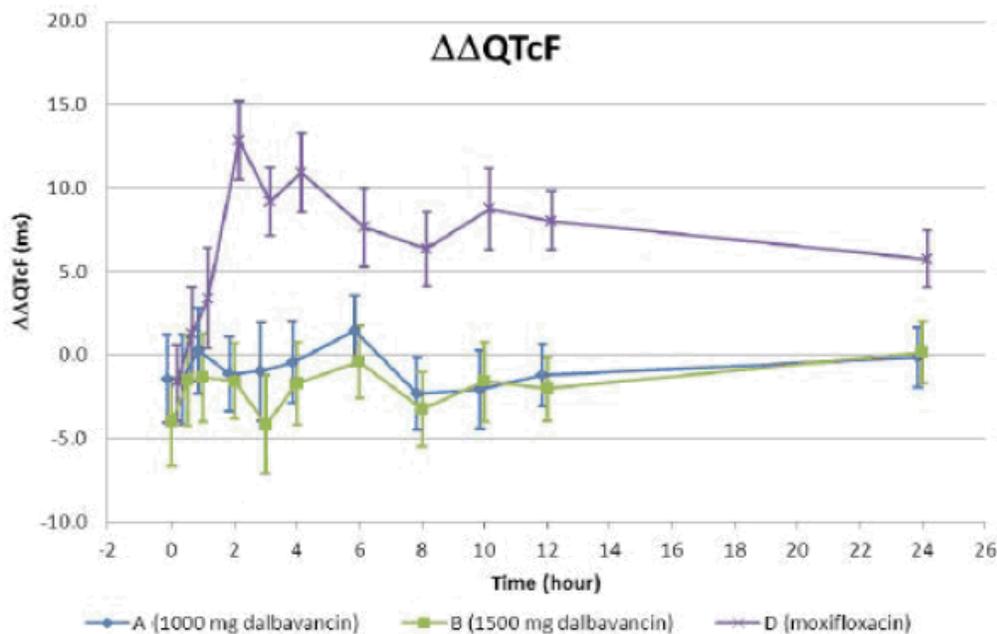
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### 2.2.3.3 Does this drug prolong the QT or QTc interval?

Preclinical studies did not indicate a high risk for a QT effect, and clinical experience with other drugs in this class (vancomycin and teicoplanin) have not suggested QT prolongation problems with glycopeptides. A thorough QT study (DUR001-102) was conducted in healthy male and female subjects receiving a single 1000 mg therapeutic dose or a single 1500 mg suprathreshold dose of IV dalbavancin. There was no significant QT prolongation detected following these doses of dalbavancin. The primary endpoint of placebo-corrected, change-from-

baseline QTcF ( $\Delta\Delta\text{QTcF}$ ), across treatments is shown in **Figure 2.2.3.3-1**, following either dose of dalbavancin and the comparator. The largest mean  $\Delta\Delta\text{QTcF}$  after dosing of dalbavancin 1000 mg was 1.5 msec (CI: -0.6 to 3.6) at 6 hours and after 1500 mg 0.2 msec (CI: -1.7 to 2.0) at 24 hours, which were significantly smaller than the one after dosing of the comparator. A small, concentration-dependent effect of dalbavancin on the  $\Delta\Delta\text{QTcF}$  was identified with an estimated slight negative population slope of -0.0051 msec/ $\mu\text{g}/\text{mL}$  and a mean intercept fixed to zero.

**Figure 2.2.3.3-1.** Placebo-Corrected Change from Time-Matched Baseline QTcF ( $\Delta\Delta\text{QTcF}$ )



For a complete assessment of the thorough QT study findings, refer to the Interdisciplinary Review Team review.

#### 2.2.4 What are the PK characteristics of the drug and its major metabolite?

The majority of clinical pharmacology studies for dalbavancin were reviewed during the original NDA submission review cycle (refer to the previous clinical pharmacology review dated 09/20/2005). The current dalbavancin NDA resubmission includes three new PK studies which were reviewed in the current cycle. Only relevant questions in section 2.2.4 are addressed.

##### 2.2.4.1 What are the single dose and multiple dose PK parameters?

The pharmacokinetics of dalbavancin were assessed in healthy subjects following the administration of single intravenous dalbavancin from 70 mg to 1120 mg and multiple dose from 300 mg on Day 1/30 mg once daily Day 2-6 to 1000 mg on Day 1/100 mg once daily Day 2-6 in the original NDA submission (refer to the previous clinical pharmacology review dated 09/20/2005). The current NDA resubmission included two PK studies evaluating 1500 mg single IV dose of dalbavancin. This review focused on the dalbavancin PK following a single 1500 mg IV.

One pilot Phase 1 study was conducted to evaluate the plasma concentration of dalbavancin following intravenous administration of a single dose of dalbavancin 1500 mg to eight (8) healthy volunteers. The mean concentration PK parameters are presented in **Table 2.2.4.1-1**. In another study evaluating dalbavancin ECG effects, the exposure and PK parameters of dalbavancin were compared following 1000 mg or 1500 mg dose (**Table 2.2.4.1-2**). The C<sub>max</sub> and AUC<sub>0-24</sub> were approximately dose-proportional. Thus, it is reasonable to consider that dalbavancin PK is linear at dose levels up to 1500 mg. A single 1500 mg dose would likely produce a dalbavancin exposure (AUC<sub>inf</sub>) similar to the proposed dosage regimen.

**Table 2.2.4.1-1.** Arithmetic mean of PK parameters following administration of a single dose of dalbavancin 1500 mg in healthy volunteers

	Arithmetic Mean (±SD)
AUC <sub>0-t</sub> (µg·hr/mL)	5202.55 (620.05)
C <sub>max</sub> (µg/mL)	467.63 (55.73)
T <sub>max</sub> * (hr)	0.50 [0.50-0.50]
Ln-Transformed	
AUC <sub>0-t</sub> (µg·hr/mL)	8.551 (0.12)
C <sub>max</sub> (µg/mL)	6.141 (0.12)

\*Mean [Range]

**Table 2.2.4.1-2.** Summary Statistics and PK Parameters of Dalbavancin Following 100 mg or 1500 mg dose.

Parameter	Arithmetic Mean (%CV) Median (Range) for t <sub>max</sub>	
	Dalbavancin IV Infusion 1000 mg N=50	Dalbavancin IV Infusion 1500 mg N=49
	AUC <sub>0-24h</sub> (µg·hr/mL)	3184.82 (12.76)
t <sub>max</sub> (hr)	0.62 (0.62–0.68)	0.62 (0.62–1.12)
C <sub>max</sub> (µg/mL)	287.32 (13.92)	422.57 (13.21)

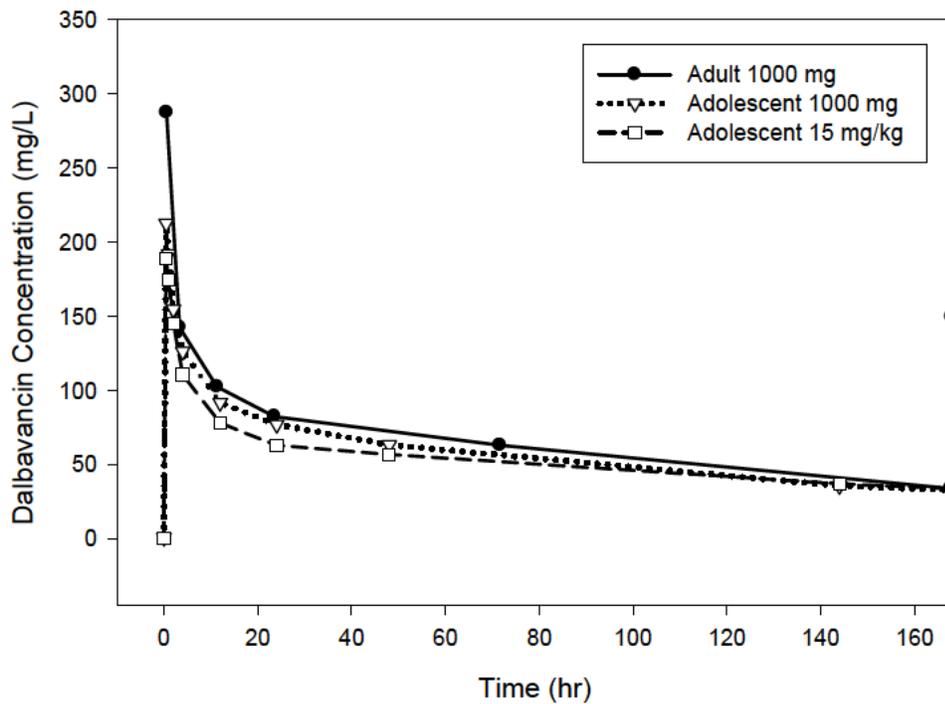
## 2.3 Intrinsic Factors

*2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

For a comprehensive review of the impact of intrinsic factors on the pharmacokinetics of dalbavancin, please refer to the previous clinical pharmacology review dated 09/20/2005. Although the sponsor is not proposing dalbavancin be labeled for treatment of ABSSSI caused by susceptible organisms, the current submission included a pharmacokinetic study in adolescent patients.

Pharmacokinetics of dalbavancin were evaluated in hospitalized adolescent (12-16 years of age) patients receiving antibiotic therapy, following single 30-min IV infusion of dalbavancin 15 mg/kg for those <60 kg or 1000 mg for those ≥60 kg (Study A8841004). The median plasma concentration-time profiles are superimposable between the two dosing groups (empty triangles and squares in **Figure 2.3.1-1**) and a summary of PK parameters in **Table 2.3.1-1**. Most of dalbavancin PK parameters were comparable, except that the mean CL, Vss and CLr appeared to be marginally higher for subjects weighing >60 kg compared to those weighing <60 kg.

**Figure 2.3.1-1.** Median dalbavancin concentration-time profiles in adolescents following 1000 mg or 15 mg/kg IV dose vs in adults following 1000 mg IV dose.



**Table 2.3.1-1.** Summary of plasma dalbavancin pharmacokinetic parameter values in adolescent patients

Parameter, Units	Parameter Summary Statistics <sup>a</sup> by Treatment	
	Dalbavancin 1000 mg	Dalbavancin 15 mg/kg
N	5	5
AUC <sub>48</sub> , µg*hr/mL	4006 (30)	3438 (26)
AUC <sub>last</sub> , µg*hr/mL	17258 (28)	15973 (21)
AUC <sub>inf</sub> , µg*hr/mL	17495 (28)	16248 (20)
C <sub>max</sub> , µg/mL	212 (12)	191 (27)
T <sub>max</sub> , hr	0.500 (0.47-1.00)	0.500 (0.47-1.00)
t <sub>1/2</sub> , hr	227 (7)	202 (20)
CL, mL/hr	57.2 (28)	48.1 (25)
V <sub>ss</sub> , mL	15232 (29)	11816 (11)
CL <sub>r</sub> , mL/hr	15.7 (37)	9.97 (48)
Ae <sub>48</sub> , µg	63705 (19)	40213 (60)
Ae <sub>48</sub> %, µg	6.37 (19)	5.31 (65)

<sup>a</sup> Geometric mean (%CV) for all except: median (range) for T<sub>max</sub>, arithmetic mean (%CV) for t<sub>1/2</sub>, Ae<sub>48</sub> and Ae<sub>48</sub>%.

<sup>b</sup> N = Number of subjects in the treatment group, n= Number of subjects contributing to the mean.

**Table 2.3.1-2** presents the summary of PK parameters in healthy adults following a single 1000 mg dose and adolescents following either a single 1000 mg or 15 mg/kg dose of dalbavancin. **Figure 2.3.1-1** depicts the mean concentration-time profiles of dalbavancin in adults and adolescents. The mean C<sub>max</sub> 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 dalbavancin concentrations were comparable in adults and adolescents receiving 1000 mg dose 12 hours post the initial dose. The population PK analysis of data from patients indicated that the population mean of CL in adults (46.0 mL/hr) appeared to be marginally lower than the mean in adolescents.

**Table 2.3.1-2.** Summary of Plasma Dalbavancin Pharmacokinetic Parameter in Adults and Adolescents

Parameter (Unit)	Adults	Adolescents (12-16 years)	
	Single 1000 mg	Single 1000 mg	Single 15 mg/kg
AUC <sub>inf</sub> (µg·hr/mL)	23443 (40.9)	17495 (28)	16248 (20)
C <sub>max</sub> (mg/L)	287 (13.9)	212 (12)	191 (27)
t <sub>1/2</sub> (hr)	346 (16.5)	227 (7)	202 (20)
CL (mL/hr)	51.3 (46.8)	57.2 (28)	48.1 (25)

Geometric mean (%CV) for all except: median (range) for T<sub>max</sub>, arithmetic mean (%CV) for t<sub>1/2</sub>.

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

*2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.*

Based upon the known exposure-response relationship for dalbavancin and comparable CL, V<sub>ss</sub>, or t<sub>1/2</sub> in adolescents (12 -16 years old) and adults in the population PK analysis (see section 4.1), the marginal differences in CL in adolescent patients compared to adults do not warrant a dosage adjustment.

#### **2.4 Extrinsic Factors**

For a comprehensive review of the impact of extrinsic factors on the pharmacokinetics of dalbavancin, please refer to the previous clinical pharmacology review dated 09/20/2005.

#### **2.5 General Biopharmaceutics**

Not applicable, as dalbavancin is intended for intravenous infusion.

#### **2.6 Analytical Section**

The bioanalytical methods included in this NDA resubmission were acceptable. For a comprehensive review of the bioanalytical methods used to determine concentrations of dalbavancin in clinical studies, please refer to the previous clinical pharmacology review dated 09/20/2005.

### **3 DETAILED LABELING RECOMMENDATIONS**

Detailed labeling recommendations will be provided in a separate addendum.

## **4 APPENDICES**

### **4.1 Individual Clinical Pharmacology Study Reviews**

**STUDY No.:** A8841004

**Title: A Phase 1, Open-Label, Single Dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Dalbavancin in Hospitalized Adolescents, Aged 12 through 17 Years Receiving Standard Intravenous Anti-Infective Treatment for Bacterial Infections**

Date(s): 25 September 2008 – 01 July 2009

Investigator(s): [REDACTED] (b) (4)

Clinical Site(s): 3 centers in the USA

Analytical Site(s): [REDACTED] (b) (4)

**OBJECTIVE(S):**

Primary: To characterize the pharmacokinetics (PK) of dalbavancin in pediatric subjects aged 12 to 17 years (inclusive) following the intravenous (IV) administration of a single dose of dalbavancin.

Secondary: To evaluate the safety and tolerability of single dose administration of dalbavancin in adolescents.

**METHODS**

**Study Design:** This was an open-label, multi-center study to investigate the PK, safety and tolerability of a single dose of IV dalbavancin in pediatric subjects aged from 12 to 17 years, inclusive (adolescents). Dalbavancin was administered to hospitalized subjects in addition to background anti-infective treatment for a known or suspected bacterial infection.

**Diagnosis and Main Criteria for Inclusion:** Hospitalized male and female subjects from 12 to 17 years of age (inclusive) receiving IV treatment for known or suspected bacterial infections.

**Study Treatment:** A single dose of 1000 mg of dalbavancin was administered to subjects weighing 60 kg or greater, and 15 mg/kg for subjects weighing <60 kg. The dose was given as a 30 minute IV infusion on Day 1. Dalbavancin for Injection, 500 mg in each vial, Lot Number 08-066155, Dosage Material Number D0803946 was supplied to all subjects at all sites.

**Analytical Methods:** Plasma and urine samples were analyzed for dalbavancin concentrations at [REDACTED] (b) (4) using a validated high-performance liquid chromatography tandem mass spectrometric method (LC/MS/MS) method, in compliance with Pfizer standard operating procedures.

Upon assay for dalbavancin plasma concentration, calibration standard responses were linear over the range of 0.500 to 500 µg/mL. The lower limit of quantification (LLOQ) for dalbavancin was 0.500 µg/mL in plasma. The between-day assay accuracy, expressed as Percent Relative Error (%RE), for Quality Control (QC) concentrations, ranged from -3.5% to 6.0%. Assay precision, expressed as the between-day coefficients of variation (CV %) of the mean estimated concentrations of QC samples was 9.9% for low (1.50 µg/mL), medium (20.0 µg/mL), high (200 µg/mL) and diluted (400 µg/mL) concentrations.

Calibration standard responses were linear over the range of 0.0500 to 50.0 µg/mL for the assay of measuring dalbavancin urine concentration. The LLOQ for dalbavancin was 0.0500 µg/mL in urine. The between-day assay accuracy (%RE), for QC concentrations, ranged from -8.8% to -2.5%. Assay precision (CV %) of the mean estimated concentrations of QC samples was 4.4% for low (0.150 µg/mL), medium (2.00 µg/mL), high (20.0 µg/mL) and diluted (40.0 µg/mL) concentrations.

*Reviewer Comment: The LLOQ of analytical methods for plasma and urine dalbavancin in the adolescent study are similar to those used in the adult PK studies. It should be noted that the LLOQ for plasma dalbavancin is higher than the MIC range (0.03-0.25 µg/mL) observed in the Phase 3 studies. The dalbavancin concentration in plasma may not be accurately determined around the MIC range.*

**Pharmacokinetic Evaluations:** Blood samples were collected via a heparin/saline lock or indwelling venous cannula from the arm contralateral to the infusion site, and immediately transferred into tubes containing di-potassium ethylenediaminetetraacetic acid. Following 10 minutes centrifuge at 1,000-1,200 × g at 4 °C, the plasma was then immediately frozen (-20°C freezer) and kept in a frozen state until assayed. Prior to the dalbavancin infusion, one aliquot (approximately 10 mL) of urine was collected as a predose sample. A 24-hour urine collection was done on Days 1 and 2. The urine samples were labeled and frozen at approximately -20°C until assayed.

Blood and urine samples for pharmacokinetic assessment were taken at the following specified timepoints (**Table 1**):

**Table 1.** Pharmacokinetic sampling scheme

<b>DAY 1</b>	<b>Plasma</b>	
	Prior to infusion	0 hour (prior to the start of the infusion)
	During infusion	0.5 hour (within 2 minutes before the end of infusion)
	Post infusion	1, 2, 4, 12 hours post-start of infusion
	<b>Urine:</b> 24-hour collection	
<b>DAY 2</b>	<b>Plasma:</b> 24 hours post-start of infusion on Day 1	
	<b>Urine:</b> 24-hour collection	
<b>DAY 3</b>	<b>Plasma:</b> 48 hours post-start of infusion on Day 1	
<b>DAY 7</b>	<b>Plasma:</b> 144 hours post-start of infusion on Day 1	
<b>DAY 14</b>	<b>Plasma:</b> 312 hours (±1 day) post-start of infusion on Day 1	
<b>DAY 21</b>	<b>Plasma:</b> 480 hours (±2 days) post-start of infusion on Day 1	
<b>DAY 28</b>	<b>Plasma:</b> 648 hours (±2 days) post-start of infusion on Day 1	
<b>DAY 56</b>	<b>Plasma:</b> 1320 hours (±4 days) post-start of infusion on Day 1	

**Safety Evaluations:** Adverse events (AEs), vital signs, physical examination and electrocardiograms (ECGs) were assessed at various timepoints throughout the study.

**Statistical Methods:** No formal inferential statistics were applied to the PK or safety data. **Table 2** presents PK parameters that were calculated. The plasma PK parameters  $AUC_{inf}$  (if data permit),  $C_{max}$ ,  $AUC_{(0-t)}$ ,  $AUC_{(48)}$ ,  $T_{max}$ ,  $CL$ ,  $V_{ss}$  and  $t_{1/2}$  were summarized descriptively by dose. Plasma concentrations were summarized descriptively by dose and PK sampling time. The urine PK parameters  $Ae_{48}$ ,  $Ae_{48}\%$  and  $CL_r$  for dalbavancin were summarized by dose.

**Table 2.** Definitions and Method of Determination of PK parameters

Parameter	Definition	Method of Determination
$C_{max}$	Maximum plasma concentration	Observed directly from data
$T_{max}$	Time for $C_{max}$	Observed directly from data as time of first occurrence
$t_{1/2}$ <sup>a</sup>	Terminal half-life	$\text{Log}_e(2)/k_{el}$ , where $k_{el}$ is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
$AUC_{48}$	Area under the plasma concentration-time profile from time zero to 48 hours postdose ( $C_{48}$ ).	Linear/Log trapezoidal method
$AUC_{last}$	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration ( $C_{last}$ )	Linear/Log trapezoidal method
$AUC_{inf}$ <sup>a</sup>	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}^*/k_{el})$ , where $C_{last}^*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
$CL$	Apparent Clearance	Dose / $AUC_{inf}$
$V_{ss}$	Apparent volume of distribution	$MRT * CL$
$Ae_{48}$	Cumulative amount of drug recovered unchanged in urine up to 48 hours	Sum of [urine concentration * sample volume] for each collection interval
$Ae_{48}\%$	Percent of dose recovered unchanged in urine up to 49 hours	$100 * (Ae_{48} / \text{Dose})$
$CL_r$	Renal clearance	$Ae_{48} / AUC_{48}$

Pharmacokinetic parameter values were calculated using an internally validated system (b) (4)

<sup>a</sup> If data permit.

## RESULTS

**Subject Disposition and Demography:** Ten subjects were assigned to study treatment, 5 subjects in the dalbavancin 1000 mg group and 5 subjects in the dalbavancin 15 mg/kg group. All subjects completed treatment and no subjects discontinued during the study. Subject demographics are summarized in **Table 3**. Ages ranged from 12 to 16 years (1000 mg mean: 14.8 years, 15 mg/kg mean: 14.2 years). Weight ranged from 61.9 to 105.2 kg in 1000 mg dose group, and from 47.9-58.9 kg in 15 mg/kg dose group.

**Table 3.** Summary of Demographics of Subjects in Study A8841004

	Dalbavancin 1000 mg			Dalbavancin 15 mg/kg		
	Male	Female	Total	Male	Female	Total
Number of Subjects	3	2	5	4	1	5
Age (years)						
12	0	1	1	1	0	1
13	0	0	0	0	0	0
14	0	0	0	2	0	2
15	2	0	2	0	1	1
16	1	1	2	1	0	1
Mean	15.3	14.0	14.8	14.0	15.0	14.2
SD	0.6	2.8	1.6	1.6	0	1.5
Range	15-16	12-16	12-16	12-16	15-15	12-16
Race						
White	2	1	3	2	0	2
Black	1	1	2	2	1	3
Weight (kg):						
Mean	65.6	101.0	79.8	51.3	55.3	52.1
SD	3.7	6.0	19.8	5.1	0	4.8
Range	61.9-69.3	96.8-105.2	61.9-105.2	47.9-58.9	NA	47.9-58.9
Body Mass Index (kg/m <sup>2</sup> )						
Mean	23.6	37.5	29.1	20.2	19.4	20.0
SD	3.1	5.1	8.3	1.7	0	1.5
Range	21.2-27.1	33.9-41.1	21.2-41.1	18.2-22.2	NA	18.2-22.2
Height (cm)						
Mean	167.3	164.5	166.2	159.5	169.0	161.4
SD	6.4	6.4	5.7	8.4	0	8.4
Range	160.0-171.0	160.0-169.0	160.0-171.0	148.0-168.0	NA	148.0-169.0

NA=not applicable

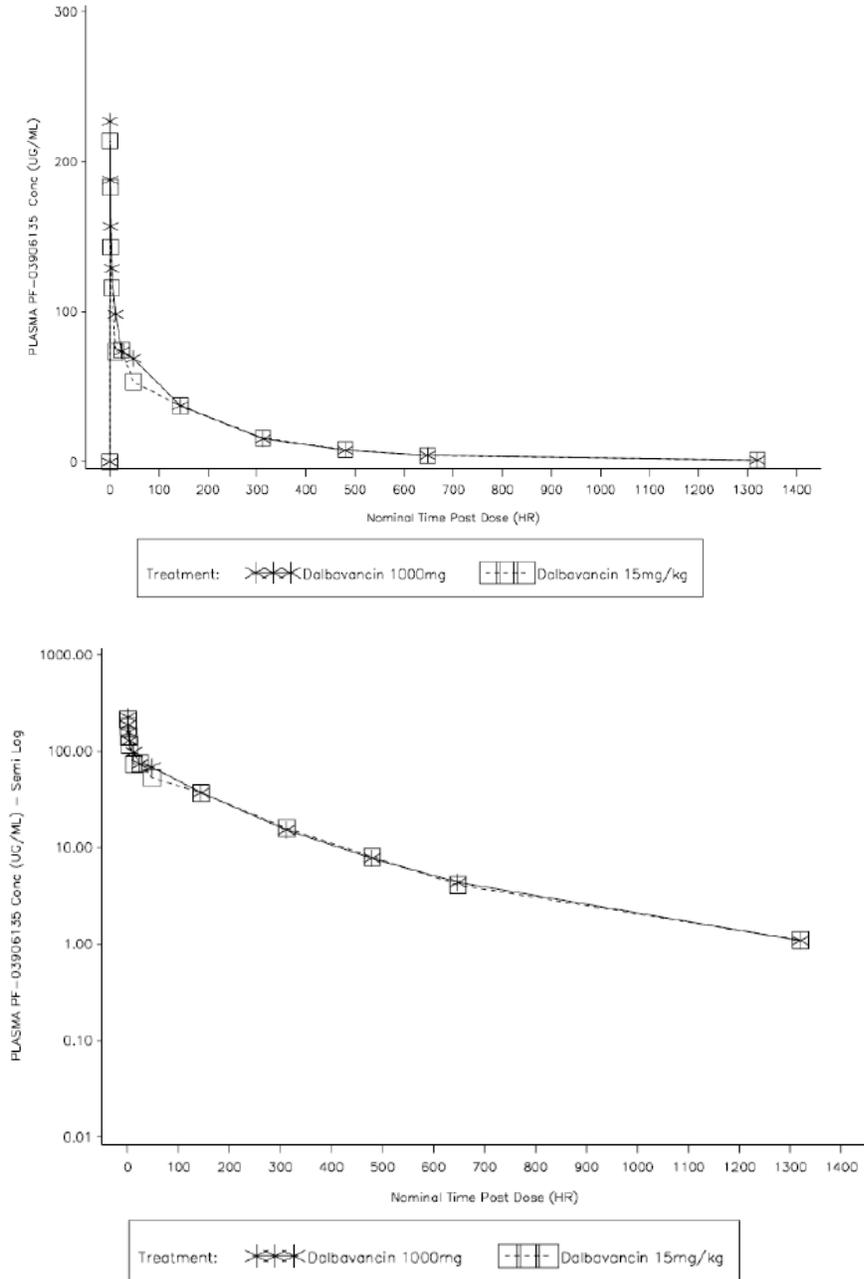
SD = standard deviation

**Pharmacokinetics:**

Protocol deviations were recorded, including subjects who entered the study even though they did not strictly meet all entrance criteria and subjects who deviated from the protocol after the start of study drug. None of these deviations were considered to have an impact on the PK or safety results.

The median plasma concentrations over time (**Figure 1**) are superimposable between the 2 treatment groups. The median  $T_{max}$  for both the treatments occurred at the end of infusion. The plasma concentrations showed a multi-phasic decline for both treatment groups, following the end of infusion. Apparent terminal  $t_{1/2}$  was similar for dalbavancin 1000 mg and dalbavancin 15 mg/kg, with mean values of 227 and 202 hours, respectively. The mean CL,  $V_{ss}$  and  $CL_r$  appeared to be marginally higher for subjects weighing >60 kg compared to subjects weighing <60 kg (**Table 4**). The total amount of dalbavancin excreted in the 48-hour period after dosing was 5-6% for both treatment groups (**Table 4**). Variability for  $AUC_{inf}$  and  $AUC_{last}$  was similar for both treatments. Individual  $AUC_{inf}$ ,  $AUC_{last}$  and  $C_{max}$  values by treatment are presented graphically in **Figure 2**.

**Figure 1.** Median dalbavancin concentration-time profiles following a single 1000 mg IV or 15 mg/kg IV dose of dalbavancin in adolescent patients (Left and right panels are linear and semi-logarithmic scales, respectively.)



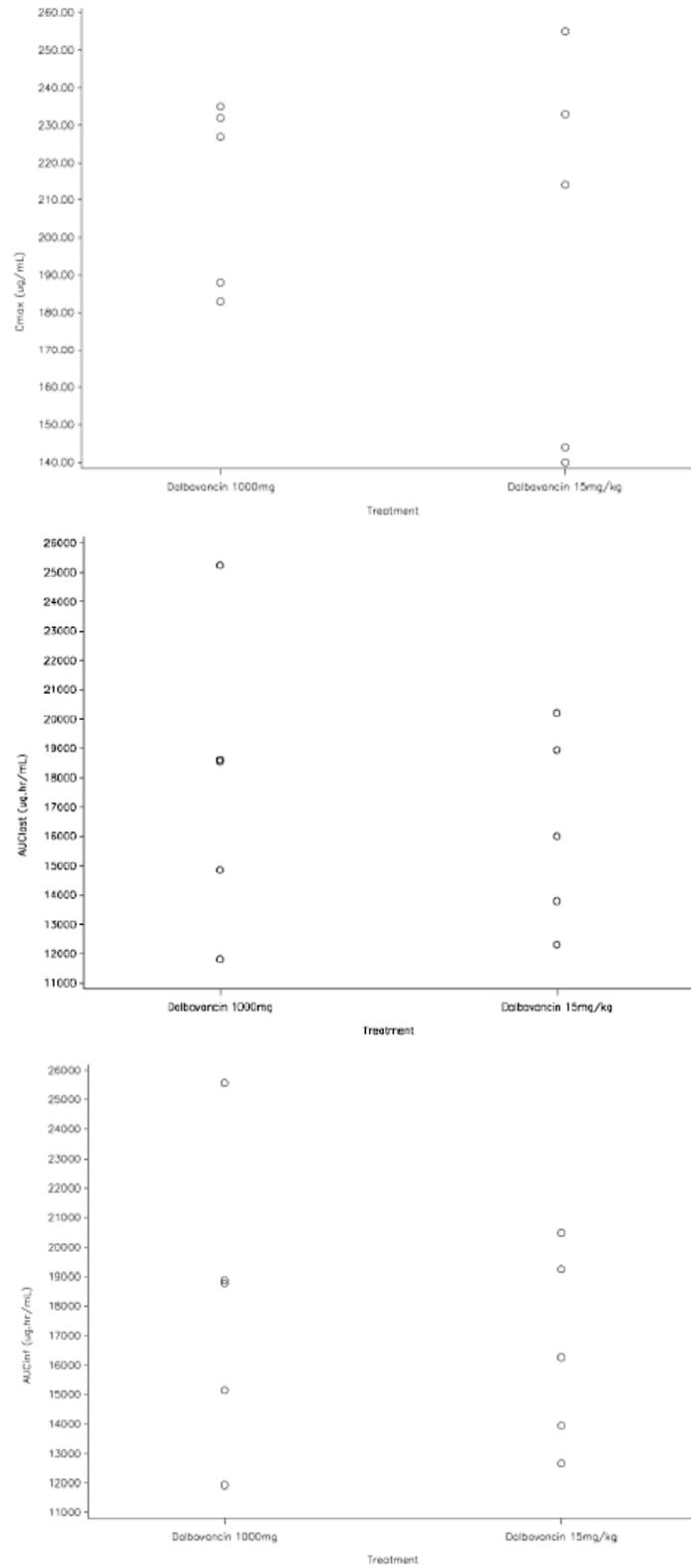
**Table 4.** Summary of plasma dalbavancin pharmacokinetic parameter values following a single 1000 mg IV or 15 mg/kg IV dose of dalbavancin in adolescent patients

Parameter, Units	Parameter Summary Statistics <sup>a</sup> by Treatment	
	Dalbavancin 1000 mg	Dalbavancin 15 mg/kg
N	5	5
AUC <sub>48</sub> , µg*hr/mL	4006 (30)	3438 (26)
AUC <sub>last</sub> , µg*hr/mL	17258 (28)	15973 (21)
AUC <sub>inf</sub> , µg*hr/mL	17495 (28)	16248 (20)
C <sub>max</sub> , µg/mL	212 (12)	191 (27)
T <sub>max</sub> , hr	0.500 (0.47-1.00)	0.500 (0.47-1.00)
t <sub>1/2</sub> , hr	227 (7)	202 (20)
CL, mL/hr	57.2 (28)	48.1 (25)
V <sub>ss</sub> , mL	15232 (29)	11816 (11)
CL <sub>r</sub> , mL/hr	15.7 (37)	9.97 (48)
Ae <sub>48</sub> , µg	63705 (19)	40213 (60)
Ae <sub>48</sub> %, µg	6.37 (19)	5.31 (65)

<sup>a</sup> Geometric mean (%CV) for all except: median (range) for T<sub>max</sub>, arithmetic mean (%CV) for t<sub>1/2</sub>, Ae<sub>48</sub> and Ae<sub>48</sub>%.

<sup>b</sup> N = Number of subjects in the treatment group, n = Number of subjects contributing to the mean.

**Figure 2.** Individual plasma dalbavancin  $AUC_{inf}$ ,  $AUC_{last}$  and  $C_{max}$  values by treatments



*Reviewer Comment: The Sponsor claimed that the dalbavancin exposure is comparable when administered as 1000 mg ( $\geq 60$  kg) or as 15 mg/kg ( $< 60$  kg) to pediatric subjects (12-16 years). This conclusion is acceptable. The mean C<sub>max</sub> in adolescents receiving 1000 mg or 15 mg/kg dalbavancin is  $>26\%$  lower than that in adults receiving single 1000 mg dose (Study DUR001-102). The variability of AUCs and C<sub>max</sub> following 1000 mg or 15 mg/kg in adolescents is also relatively large, compared to dalbavancin PK parameters in the Phase 1 studies in healthy adults (Study VER001-1 and VER001-2).*

## Safety

A summary of adverse events (AEs) is presented in **Table 4**. Five subjects in the dalbavancin 1000 mg group and 4 subjects in the 15 mg/kg group experienced AEs. There were no treatment-related AEs and no severe AEs. There were no temporary or permanent discontinuations or dose reductions of treatment due to AEs. AEs experienced in the 1000 mg group were diarrhea, nausea, vomiting, increased blood bilirubin, headache, nasal congestion and hypotension. AEs experienced in the 15 mg/kg group were abdominal pain, constipation, ileus, hyperbilirubinemia, skin laceration, wound, dehydration, dizziness, headache and rash macular. The only AE of moderate severity was headache in the 1000 mg group; all other AEs were of mild severity.

None of the electrocardiogram (ECG) measurements were consider clinically significant. Moreover, none of the subjects presented with observed QTc values  $>480$  msec or exhibited change scores  $>60$  msec within this study.

**Table 4.** Summary of treatment-emergent adverse events

	Dalbavancin 1000 mg N=5		Dalbavancin 15 mg/kg N=5	
	All Causality	Treatment-Related	All Causality	Treatment-Related
Number of AEs	7	0	10	0
Subjects with AEs	5	0	4	0
Subjects with SAEs	0	0	1	0
Subjects with severe AEs	0	0	0	0
Subjects who discontinued due to AEs	0	0	0	0
Subjects who dose reduced or temporary discontinuations due to AEs	0	0	0	0

Four subjects in the 1000 mg group and 4 subjects in the 15 mg/kg group were reported to have laboratory test abnormalities without regard for baseline value. Decreased hemoglobin was reported for 2 subjects in the 15 mg/kg group, and urine blood, urine red blood cells, urine white blood cells and urine bacteria was reported for 1 subject in the 1000 mg group and 2 subjects in the 15 mg/kg group; all other laboratory test abnormalities were only experienced by 1 subject in either group.

*Reviewer Comment: The most commonly observed adverse events in adult clinical studies include nausea, diarrhea, headache, constipation, and vomiting. The observation of AEs in the adolescent patients was similar to those in adults.*

**SPONSOR'S CONCLUSIONS:**

- Mean plasma exposures for dalbavancin, based on  $AUC_{inf}$  and  $C_{max}$ , were similar when administered as 1000 mg to pediatric subjects (12-16 years) weighing >60 kg (61.9-105.2 kg) or as 15 mg/kg to pediatric subjects weighing <60 kg (47.9-58.9 kg).
- Apparent terminal  $t_{1/2}$  was similar for dalbavancin dosages of 1000 mg and 15 mg/kg, with mean values of 227 and 202 hours, respectively.
- The safety profile of dalbavancin in the subjects aged between 12 and 16 years in this study was acceptable.

**REVIEWER ASSESSMENT:** The mean of AUC or  $C_{max}$  following 1000 mg ( $\geq 60$  kg) or 15 mg/kg (<60 kg) is relatively lower than those in adults. However, the differences observed between adolescents and adults are not conclusive, due to the variability of PK parameters across adult studies (Study VER001-1, VER001-2, VER001-11, VER001-12, and VER001-13). The mean of CL,  $V_{ss}$ , or  $t_{1/2}$  in adolescents (12 -16 years old) is comparable to that in adults, according to the population PK analysis. Moderate variability in pharmacokinetic parameters was observed in adolescents (12-16 years old). The PK data from this adolescent study were not included in the population PK analysis. Overall, the Sponsor's conclusions appear appropriate based on study results.

**STUDY No.:** DUR001-101

**Title: A Pilot Study to Determine Plasma Concentrations Following Administration of Dalbavancin 1500 mg by Intravenous Infusion in Healthy Volunteers**

Date(s): 30 March 2011 – 11 April 2011

Investigator(s):

[REDACTED] (b) (4)

Study Center(s): Cetero Research, 4801 Amber Valley Parkway, Fargo, ND 58104, USA

Analytical Site(s):

[REDACTED] (b) (4)

**OBJECTIVE(S):**

This study evaluated the plasma concentrations of dalbavancin following intravenous administration of a single dose of dalbavancin 1500 mg to healthy volunteers.

**METHODS**

**Study Design:** This was an open-label, single-dose, one-period, one-treatment study under fasted conditions. Eight healthy adult subjects (male and female) were enrolled in the study. The total duration of the study, screening through study exit, was approximately 6 weeks. The subjects received a single dose of dalbavancin 1500 mg on Day 1.

**Pharmacokinetics:** Blood sample collections were obtained within 90 minutes prior to each subject's scheduled dose time (0 hour), 20 minutes after the start of the infusion, immediately following the end of the infusion (0.5 hour), and at 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the start of the infusion.

**Safety:** Adverse events were recorded throughout the study, reported spontaneously and in response to queries every 12 hours throughout the confinement period of the study, prior to being released from confinement, and during the follow-up phone visit by phone call at Day 14 ( $\pm 3$ ). All subjects underwent clinical laboratory testing at screening, including hematology, clinical chemistry, urinalysis, urine drug and cotinine screen, serology, and for women, a pregnancy screen and FSH. An electrocardiogram (ECG) was recorded at screening.

**Inclusion Criteria:** Eight healthy, non-smoking, adult male and female volunteers 18-55 years of age, were enrolled in this study. Body mass index (BMI) was between 18 and 32 kg/m<sup>2</sup>, and body weight was at least 110 lbs.

**Treatment:** Each subject received dalbavancin 1500 mg as a single-dose, 30 ( $\pm 2$ ) minute intravenous (IV) infusion. Total study period, exclusive of screening, was 12 days. **Table 1** illustrates the PK sampling, laboratory and safety assessments at screening and over the course of the study.

**Table 1. Study Schematic**

TRIAL PHASE	Screening Day -28 to Day -1	CONFINEMENT AND RETURNS AT CLINICAL RESEARCH UNIT			Early Termination or Study Exit
		Check-in Day -1	Treatment Day 1	Day 2	
Screening Consent Form	X				
Informed Consent	X	X <sup>a</sup>			
Eligibility (Inclusion/Exclusion)	X	X <sup>a, b</sup>			
Prior Medication Assessment	X	X <sup>b</sup>			
Medical History	X	X <sup>b</sup>			
Vital Signs	X		X <sup>c</sup>	X <sup>c</sup>	X
12-lead ECG	X				
Physical Examination	X <sup>a</sup>				X <sup>d</sup>
Clinical Laboratory Tests	X <sup>e</sup>				X <sup>e</sup>
Serology Screen	X				
Pregnancy Screen (females only)	X	X			X
FSH (if necessary to document postmenopausal status)	X				
Urine Drug Screen	X	X			
Urine Cotinine Screen	X	X			
Study Drug Administration			X		
Pharmacokinetic Sampling			X <sup>f</sup>	X <sup>f</sup>	X
Follow-up Phone Call					X <sup>g</sup>
Adverse Events Query			X	X	X
Concomitant Medication Query			X	X	X

<sup>a</sup> If not already completed at screening

<sup>b</sup> Updated and/or reviewed

<sup>c</sup> Seated blood pressure, heart rate, and respiratory rate were measured prior to dosing and at 1, 12, and 24 hours after the start of the infusion. Oral temperature was taken prior to dosing and at 1, 6, 12, 18, and 24 hours after the start of the infusion.

<sup>d</sup> If requested by the Investigator

<sup>e</sup> CBC with differential and clinical chemistry were performed at screening and at the end of study confinement period. Urinalysis was performed at screening.

<sup>f</sup> Pharmacokinetic sampling occurred within 90 minutes prior to each subject's scheduled dose time (0 hour), 20 minutes after the start of the infusion, immediately following the end of the infusion, and at 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the start of the infusion.

<sup>g</sup> A follow-up phone call was performed 14 (±3) days after dose administration.

**Analytical Methods:** Dalbavancin plasma concentrations were measured using a liquid chromatography with tandem mass spectrometry (LC/MS/MS) method validated at (b) (4) prior to sample analysis. The plasma samples were collected from March 31, 2011 to May 11, 2011. According to the bioanalytical report, 104 human plasma samples and 104 duplicate samples were received frozen on dry ice for analysis on (b) (4). Sample analysis was performed from (b) (4). Frozen stability has been proven for 63 days at -20°C. The dalbavancin concentrations ranged from below the limit of quantitation (LOQ <1.00 µg/mL) to 554 µg/mL. Overall precision

for the quality control samples, as measured by %RSD, was  $\leq 10.8\%$ . The overall accuracy as measured by %RE, for these quality control samples ranged from  $-7.25\%$  to  $7.33\%$ . The precision for the 10-fold dilution integrity quality control samples was  $4.06\%$ . The accuracy for the 10-fold diluted quality control samples was  $5.00\%$ .

**Pharmacokinetic Assessment:** Pharmacokinetic parameters for dalbavancin were calculated using standard noncompartmental approaches as indicated below:

**AUC<sub>0-t</sub>:** The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.

**C<sub>max</sub>:** Maximum measured plasma concentration over the time span specified.

**T<sub>max</sub>:** Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, T<sub>max</sub> was defined as the first time point with this value.

Data from subjects with missing concentration values may have been used if PK parameters could have been estimated using the remaining data points.

Reviewer Comments:

*The 1500 mg dalbavancin dose in this study is the same as the supratherapeutic dose in the thorough QT/QTc study of dalbavancin (Study DUR001-002). The bio-analytical method used to assess dalbavancin concentration is appropriate.*

**RESULTS**

**Study Population:** Eight (8) healthy non-smoking subjects (4 males and 4 females) were enrolled in the study. Mean demographic data with standard deviations for all subjects, are presented in **Table 2**.

**Table 2.** Summary of Demographic Data

Parameters	All Subjects N = 8	Females N = 4	Males N = 4
Age	32.9 (19 - 55)	31.5 (20 - 43)	34.3 (19 - 55)
Weight (lbs)	159.3 (118.6 - 197.2)	141.3 (118.6 - 172.8)	177.4 (168.8 - 197.2)
Height (in.)	66.5 (59.0 - 74.9)	63.0 (59.0 - 65.7)	70.0 (66.2 - 74.9)
BMI	25.3 (21.4 - 28.8)	25.0 (21.8 - 28.5)	25.7 (21.4 - 28.8)
Race <sup>1</sup>			
Asian:	1 (12.5%)	1 (25.0%)	-
African American:	-	-	-
Native Hawaiian or Other Pacific Islander:	-	-	-
American Indian or Alaskan Native:	-	-	-
White:	7 (87.5%)	3 (75.0%)	4 (100.0%)

<sup>1</sup>Subjects used in final statistical report.

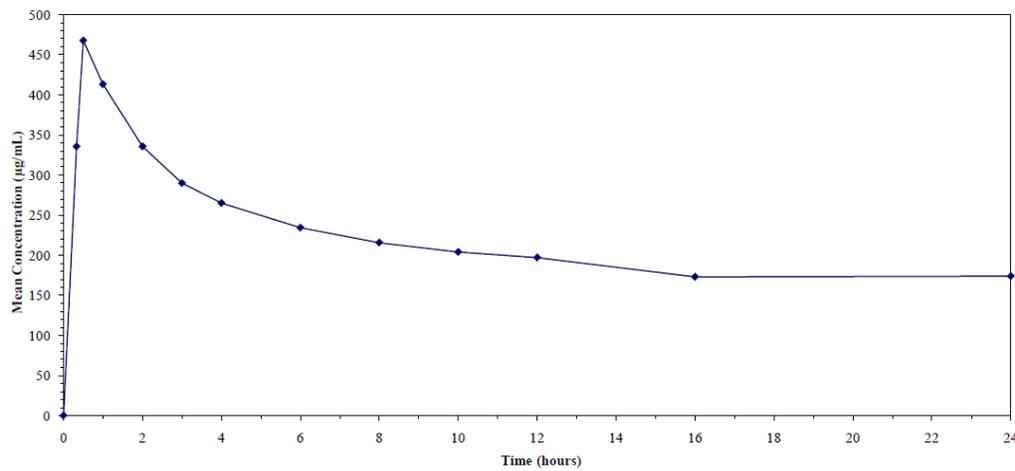
**Pharmacokinetics:** The analytical data were used to calculate the following PK parameters: AUC<sub>0-t</sub>, C<sub>max</sub>, and T<sub>max</sub>. **Table 3** presents the mean ( $\pm$ SD) or range for all parameters. No protocol deviations were identified. Mean and individual dalbavancin plasma concentration-time plots following a single 1500 mg IV dose are presented in Figures 1 and 2, respectively.

**Table 3.** Arithmetic mean of PK parameters

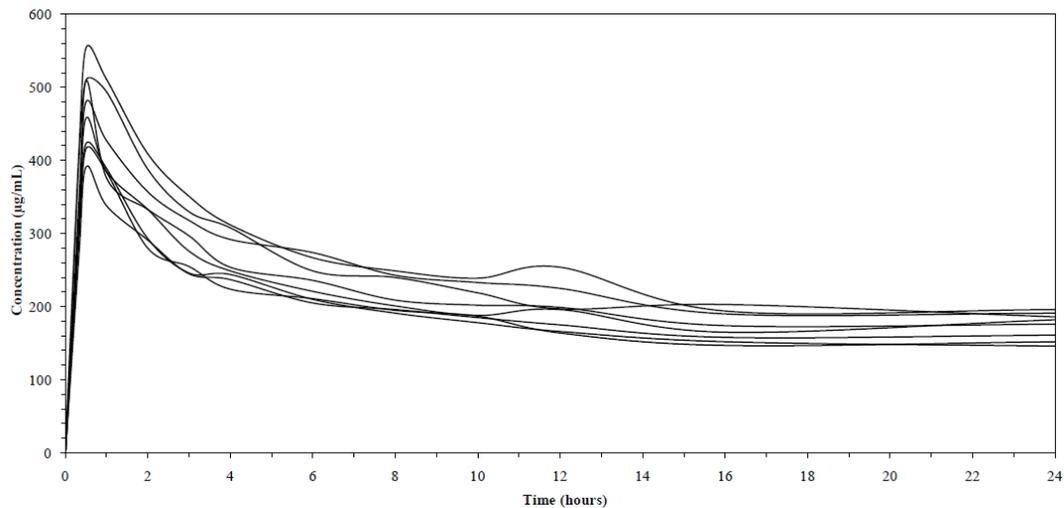
	Arithmetic Mean ( $\pm$ SD)
AUC <sub>0-t</sub> ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	5202.55 (620.05)
C <sub>max</sub> ( $\mu\text{g}/\text{mL}$ )	467.63 (55.73)
T <sub>max</sub> * (hr)	0.50 [0.50-0.50]
Ln-Transformed	
AUC <sub>0-t</sub> ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	8.551 (0.12)
C <sub>max</sub> ( $\mu\text{g}/\text{mL}$ )	6.141 (0.12)

\*Mean [Range]

**Figure 1.** Dalbavancin mean plasma concentration (0 - 24 hours) (N=8) following a single 1500 mg dose as a 30-min IV infusion (Top: Linear scale; Bottom: Semi-logarithmic scale)



**Figure 2.** Dalbavancin plasma concentrations (0 - 24 hours) for each subject (N=8) following a single 1500 mg dose as a 30-min IV infusion



Reviewer Comment:

*The half-life of dalbavancin is over 200 hours. So, ideally, a PK study should have a prolonged sampling time period (e.g. over 800 hours). Presentation of  $AUC_{0-inf}$  and  $t_{1/2}$  based on the prolonged sampling time period may be more appropriate, rather than  $AUC_{0-24}$  in this case. This study had PK samples from 0 to 24 hours, which would not be able to cover the entire drug elimination phase. However, another study (DUR001-102) with larger sample size indicated that the PK profiles were superimposable following 1000 mg and 1500 mg IV administration and the  $AUC_{0-24}$  and  $C_{max}$  were proportionally increased. Thus, the PK results of the present study with single 1500 mg dose are acceptable.*

**Safety:**

Four subjects experienced a total of 9 AEs over the course of the study. The AEs were mild to moderate in intensity. A total of 7 mild and 2 moderate AEs occurred in subjects after they received the test product under fasted conditions. There were no deaths, other SAEs, or discontinuations of study drug due to an AE in this study. No clinically significant change in laboratory parameters or vital signs was considered to be clinically significant by the Investigator.

**SPONSOR'S CONCLUSIONS:** The following PK parameters for dalbavancin were determined following an intravenous dose of 1500 mg (infused over  $30 \pm 2$  minutes) administered to healthy volunteers in this pilot study: the mean  $AUC_{0-24}$  was calculated as 5202.55  $\mu\text{g}\cdot\text{hr}/\text{mL}$ , the mean  $C_{max}$  was 467.63  $\mu\text{g}/\text{mL}$ , and the mean  $T_{max}$  was at the end of the 30 minute infusion. Overall, dalbavancin was well tolerated as a single intravenous dose of 1500 mg administered to healthy adult subjects under fasted conditions.

**REVIEWER ASSESSMENT:** This Phase 1 study does not provide complete dalbavancin PK information following single 1500 mg IV dose, due to limitations of sampling. However, dalbavancin exposures produced by single 1000 mg and 1500 mg IV administration were also evaluated in Study DUR001-102. Collectively the PK information of these two studies (Study DUR001-101 and DUR001-102) and the Sponsor's conclusions are acceptable.

(b) (4)



## 4.2 Pharmacometric Review

# PHARMACOMETRIC REVIEW

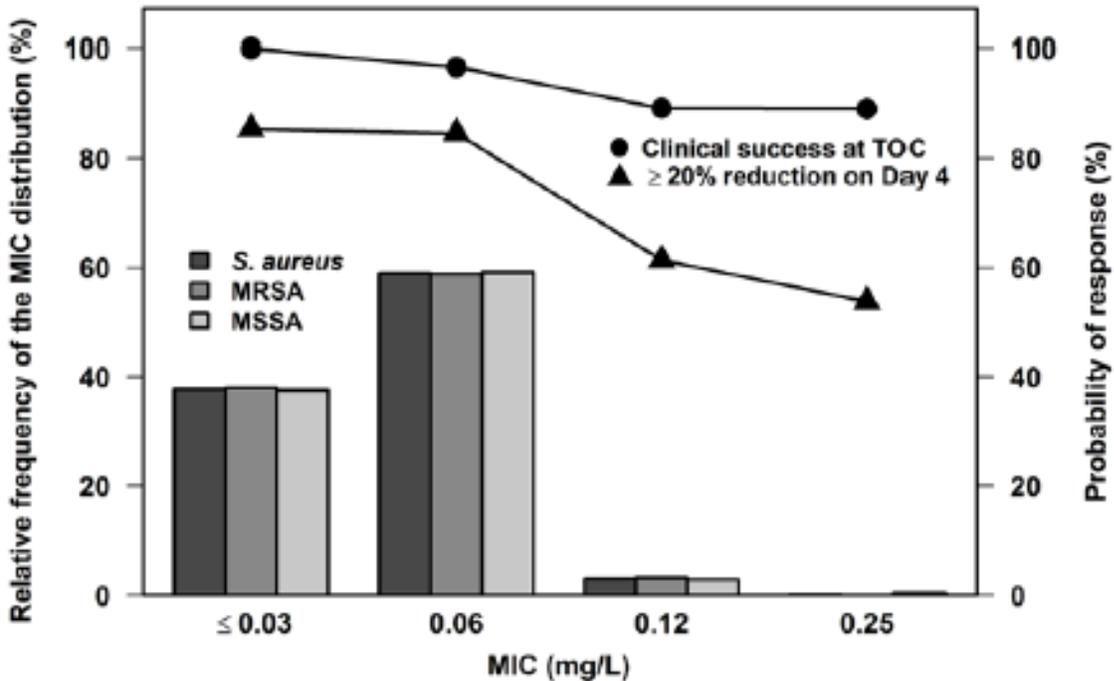
## 1 SUMMARY OF FINDINGS

A total of 1668 dalbavancin concentrations from 532 subjects from three Phase 2/3 studies were included in the population pharmacokinetic (PopPK) 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 total clearance (CL) was 0.046 L/hr and the population steady state volume of distribution ( $V_{ss}$ ) was 20.85 L. Body surface area (BSA) and creatinine clearance (CRCL) were the most influential covariates, with BSA included on CL, central volume of distribution ( $V_c$ ) and peripheral volume of distribution ( $V_p1$ ) and CRCL included on CL. Albumin, sex, and age were also important covariates but not considered to be as clinically important as BSA and CRCL. Pharmacometric analyses for dalbavancin were conducted using individual predicted exposures ( $AUC_{avg}$ , defined as  $AUC_{0-120hr}/5days$ ) and efficacy endpoints from one Phase 3 study in patients with acute bacterial skin and skin structure infection (ABSSSI) administered intravenous (IV) dalbavancin 1000 mg on Day 1 and 500 mg on Day 8. The univariable analyses conducted by the Sponsor indicated that:

- $AUC_{avg}/MIC$  of equal or greater than 13,658, 14,472, and 21,267 was associated with a higher percentage of patients achieving microbiological success at End of Therapy (EOT), clinical success at Test of Cure (TOC), or microbiological success at TOC (90.9%, 98.4%, or 92.6%, respectively).
- $AUC_{avg}/MIC$  of equal or greater than 16,096, 13,396, or 14,320 was significantly associated with a higher percentage of patients achieving  $\geq 10$ , 20, or 30% reduction from baseline in the area of infection on Day 4 (91.3%, 86.3%, or 81.3%, respectively).

The relationship between  $AUC_{avg}/MIC$  and clinical response at TOC was used by the Sponsor to inform in vitro interpretive criteria determination for dalbavancin against *Staphylococcus aureus*. Based on the sponsor's analysis of  $AUC_{avg}/MIC$  and clinical response at TOC, the mean model-predicted percent probability of a successful clinical response exceeded or approached 90% up to an MIC value of 0.25 mg/L. Thus, the Sponsor proposed a susceptibility breakpoint of at least 0.25 mg/L for dalbavancin against *S. aureus*. Graphical display of this relationship and a tabulated summary of predicted responses at various MIC intervals for clinical success at TOC are shown below in **Figure 1.1.2-1**

**Figure 1.1.2-1.** Mean model-predicted percent probabilities of response by MIC overlaid over MIC distributions for *S. aureus*



**Table 1.1.2-1.** Mean Model Predicted Probabilities of Response by MIC Value for Dalbavancin against *S. aureus*

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

However, the modeled relationship for the clinical success at TOC may be not robust enough to support breakpoint determination due to the low number of subjects with MIC values >0.06 mg/L included in the analysis. The number of pathogens with MIC of >0.25 mg/L, the sponsor’s proposed breakpoint, was less than 0.2% of the population, which may bias predictions of the probability of achieving clinical success at TOC for patients infected with isolates with MICs greater than or equal to 0.25 mg/L. This limited data may also have contributed to the Sponsor only being able to identify a dichotomous AUC/MIC threshold from the PK-PD analysis rather than a continuous relationship. The ramifications of this dichotomous PK-PD relationship are that response rates from the simulations are bounded based on the observed response rate in subjects above and below the threshold value. This is depicted above in the **Table 1.1.2-1** where the mean model-predicted percent probability of response for clinical success and ≥20%

reduction in lesion size on Day 4 was 100% and 85.4% for an MIC of 0.03 mg/L and 89.1% and 53.8% for an MIC of 0.25 mg/L.

Applying these simulation results to determine the dalbavancin breakpoint by identifying a decrease in clinical response rate below 90% based on the simulation results may be inappropriate. Interpretation of the simulation results should instead focus on a major inflection from a higher to a lower clinical response rate, MIC values of 0.06 and 0.12 mg/L in the dalbavancin case.

It should also be noted that the current FDA guidance for ABSSSI treatment recommends that primary efficacy endpoints should be  $\geq 20\%$  reduction in the lesion size at 48 to 72 hours compared to baseline. Thus, additional exploratory analyses were performed by the reviewer to understand the suitability of these early efficacy endpoints in determination of dalbavancin breakpoints in comparison with the already mentioned clinical success endpoint, after assessing overall acceptability of the Sponsor's PopPK model and PK-PD relationships.

In the reviewer's exploratory analysis, the predicted PK-PD relationships for all reported efficacy endpoints, including clinical success and microbiological success at TOC or EOT, and  $\geq 10$ ,  $\geq 20$ , and  $\geq 30\%$  lesion size reductions on Day 4, were used for derivation of probabilities of responses for each MIC. Similar pattern of the predicted probability of achieving clinical endpoint versus MICs was observed for all clinical outcomes on Day 4, although predicted probabilities were below the conventionally used value of 90% for these clinical outcomes.

Substantial decreases in the predicted probability of achieving clinical endpoint were observed beyond an MIC of 0.06 mg/L for all efficacy endpoints of lesion size reductions on Day 4.

Altogether, we conclude that the breakpoint for dalbavancin against *S. aureus* can be informed by the PK-PD relationship for the efficacy endpoint of percentage reduction from baseline in the area of infection on Day 4. The reviewer recommends a lower dalbavancin breakpoint of 0.06 mg/L against *S. aureus*, instead of 0.25 mg/L as proposed by the Sponsor. However, it should be noted that the determination of breakpoints involves multiple disciplines providing clinical and microbial interpretations in addition to the above PK-PD observations. The ultimate determination of the dalbavancin breakpoint should depend on the totality of information provided by each discipline and continues to be assessed as of the completion of this review.

## 2 BACKGROUND

Dalbavancin is a second generation lipoglycopeptide antibiotic. It is currently being developed for use in skin and skin structure infections (SSSI) involving Gram-positive bacteria such as staphylococci and streptococci, including many antibiotic-resistant organisms. The sponsor proposed that the recommended dosing regimen for dalbavancin is 1000 mg IV on Day 1 and 500 mg IV on Day 8. Dosage adjustment is needed for patients with severe renal insufficiency (creatinine clearance <30 mL/min), and the proposed dose is 750 mg IV on Day 1 and (b) (4) IV on Day 8. The Phase 3 clinical study for the treatment of patients with complicated SSSI (VER001-09) demonstrated that dalbavancin was well-tolerated and had comparable clinical efficacy to linezolid (88.9% success for dalbavancin, 91.2% success for linezolid) at test-of-cure visits (primary efficacy endpoint). The new Phase 3 clinical trials (DUR001-301/302) for the treatment of patient with acute bacterial SSSI showed that the proportion of patients considered a clinical responder at 48 to 72 hours was similar between patients in the dalbavancin (83.3%) and the comparator (vancomycin/linezolid, 81.8%) treatment groups and clinical success rates at end-of-treatment (EOT) were comparable between these treatment groups.

## 3 RESULTS OF SPONSOR'S ANALYSIS

### 3.1 Population PK analysis (POP-PK-PROJ-2013)

#### 3.1.1 Objectives:

- Describe the PK of dalbavancin administered to patients using a population approach.
- Estimate the impact of physiological and demographic factors that may affect dalbavancin PK in this population. This investigation primarily focused on the covariate effects for gender, age, and weight although other covariates were also evaluated.

#### 3.1.2 Studies included in the PopPK analysis

Since the two newly completed Phase 3 studies did not include assessment of dalbavancin PK, the data used in the population analysis (POP-PK-PROJ-2013) only included all available concentration data collected from Studies VER001-4 (n=30), VER001-5 (n=34), and VER001-9 (n=468), which are the same as the previous population PK analysis (VER001-PK-001, 06/10/2004). Briefly, in VER001-4, patients with catheter-related blood stream infections were randomized to receive dalbavancin IV 650 mg loading dose on Day 1 followed by daily maintenance doses of 65 mg for up to 13 days, a 1000 mg loading dose on Day 1 and a single 500 mg dose on Day 8, or comparator. In VER001-5, patients with uncomplicated and complicated skin and skin structure infections received dalbavancin IV 1100 mg single dose, dalbavancin 1000 mg on day 1 followed by 500 mg on day 8, or comparator. In VER001-9, patients with complicated and skin and skin structure infections were randomized to receive dalbavancin IV 1000 mg on day 1 and 500 mg on day 8, or comparator. Demographic details of the patients included in the pharmacokinetic analysis are shown in **Table 3.1.2-1**.

**Table 3.1.2-1. Demographic Details of Patients Included in the PopPK Analysis**

Demographic	Mean (SD)	Median (range)	Number (percentage)
Age (years)	47.4 (16.3)	46 (18 – 93)	-
Weight (kg)	91.7 (28.5)	88 (42.8 – 320)	-
Height (m)	1.71 (0.128)	1.71 (1.12 – 2.67)	-
Body surface area (m <sup>2</sup> )	2.07 (0.330)	2.05 (1.36 – 4.00)	-
Lean body weight (kg)	57.9 (13.1)	57.9 (30.3 – 99.1)	-
Body mass index (kg/m <sup>2</sup> )	31.4 (9.86)	29.3 (8.65 – 98.8)	-
<u>Sex (numerical code)</u>	-	-	315 (59.2)
Male (0)			217 (40.8)
Female (1)			
<u>Race (numerical code)</u>	-	-	
Black (1)			65 (12.2)
Asian (2)			5 (0.94)
Caucasian (3)			350 (65.8)
Hispanic (4)			103 (19.3)
Other (5)			9 (1.69)
Albumin (g/dL)	3.53 (0.643)	3.60 (1.10 – 5.10)	-
Serum creatinine (mg/dL)	0.924 (0.289)	0.900 (0.400 – 2.88)	-
Creatinine clearance (mL/min) <sup>*</sup> (CRCL)	115 (31.6)	121 (26.0 – 150)	-
Creatinine clearance (mL/min) <sup>†</sup> (CRCLLBW)	81.2 (30.8)	79.1 (14.6 – 225)	-

Source: Demographics.xls

Abbreviations: CRCLLBW = creatinine clearance evaluated using lean body weight; SD = standard deviation

<sup>\*</sup>Based on the Cockcroft and Gault formula using total body weight as the size descriptor, capped at 150 mL/min

<sup>†</sup>Based on the Cockcroft and Gault formula using lean body weight as the size descriptor

**Reviewer’s comment:**

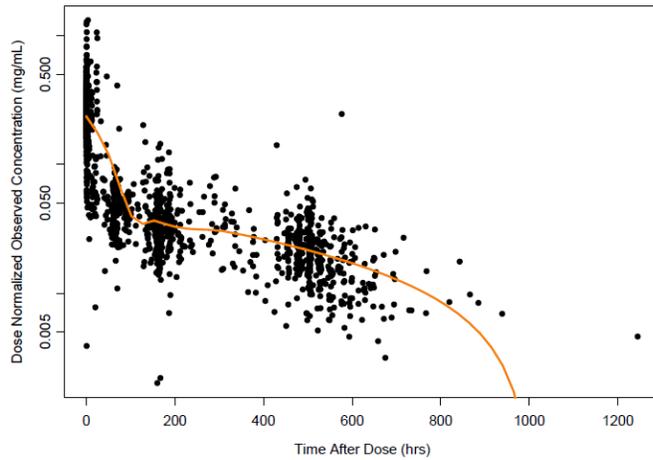
*The range of age and body weight of patients included in the analysis was wide, and the patient population was well balanced between genders, which assisted in assessing the impact of covariates in the subsequent analysis. The range of creatinine clearance values in the population PK analysis included subjects with normal, mild, and moderate renal impairment (n<8).*

**3.1.3 Methods and Results**

• **Description of Data Included in the Analysis**

The final dataset consists of a total of 1668 concentrations from 532 subjects who received dalbavancin in three aforementioned Phase 2/3 studies. The dosage regimens included IV 650 mg loading dose on Day 1 and daily maintenance doses of 65 mg for up to 13 days, 1000 mg on Day 1 and 500 mg IV dose on Day 8, 1100 mg IV single dose. Observations that were below the quantitation limit (BQL) for dalbavancin were not included. The observed concentration-time profiles from all patients were depicted in **Figure 3.1.2-1**.

**Figure 3.1.3-1** Observed dalbavancin dose normalized concentrations in Log-linear scale. The solid line is Loess smooth of the observed dalbavancin concentrations.



- **Sponsor's Base model**

The best structural model to describe the PK of dalbavancin was a 3-compartment model with zero order input and first order elimination (**Figure 3.1.3-1**).

(b) (4)

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***Overall Reviewer's Comment for Population PK Analysis:***

*The base model and the final covariate model are reproducible, but parameter estimation was found to be sensitive to initial values. Several issues are identified in the model building and model validation processes, as indicated previously in the Reviewer's Comments. In addition, one limitation of the model is that dalbavancin renal clearance could not be independently*

estimated by the model due to the lack of urinary excretion data collected for any of the Phase 2/3 patients. The model estimated parameter ( $\theta_2$ ) can be considered as a parameter describing contribution of CRCL to the total CL. Based on the reviewer's assessment, the Sponsor's population PK model provides an acceptable description of plasma concentration-time profiles for dalbavancin for the purpose of breakpoint determination at this stage of development. The dalbavancin exposure simulated for patients using this model can be used to further assess the exposure-response relationship.

### 3.2 Exposure-Response Analysis

The sponsor conducted an exposure-response (E/R) analysis using clinical response data from Study VER001-9 for purposes of determining interpretive susceptibility criteria. The sponsor refers to this analysis as a "PK-PD" analysis. Conventional terminology for target attainment analyses using nonclinical PK/PD targets is also referred to as "PK/PD" analyses. The remainder of this review will refer to the former to be consistent with the sponsor.

#### 3.2.1 Introduction

A population PK analysis was performed using data from Studies VER001-4, VER001-5 and VER001-9. As described in 3.1, the final model was a three-compartment model with zero-order input and linear elimination. BSA and CRCL were found to significantly impact dalbavancin PK. These PK-PD analyses included individual predicted exposures based on the above population PK model and efficacy data for dalbavancin from Study VER001-9, a Phase 3 study in patients with ABSSSI who received intravenous (IV) dalbavancin 1000 mg on Day 1 and 500 mg on Day 8. The objectives of these analyses were:

1. To characterize pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy; and
2. Using the results of PK-PD analyses for efficacy and Monte Carlo simulation, to conduct analyses to provide decision support for establishing *S. aureus* in vitro susceptibility interpretive criteria for dalbavancin.

#### 3.2.2 Methods

- **Analysis Populations**

The analysis population consisted of patients with ABSSSI enrolled in Study VER001-9 who received dalbavancin, who were in the EOT and/or TOC microbiologically evaluable (ME) populations, and for whom pharmacokinetic (PK) data were available (n=192). Proportion of the analysis population was 41% of the patients with PK data. Patients for whom clinical response was declared to be a failure for reasons other than those related to efficacy were excluded from the analysis population. A subset of the patients with ABSSSI due to *S. aureus* was evaluated as a separate analysis population. **Table 3.2.2-1** summarizes demographics of these evaluable populations.

**Table 3.2.2-1** Summary statistics of categorical baseline patient demographic and disease characteristics

Variable	All patients (N=192) % (n)	Patients with <i>S. aureus</i> (N=177) % (n)
<b>Race/Ethnicity</b>		
African American	12.5 (24)	13.0 (23)
Caucasian	64.6 (124)	64.4 (114)
Hispanic/Latino	19.8 (38)	19.2 (34)
Other	3.1 (6)	3.4 (6)
<b>Sex</b>		
Male	61.5 (118)	60.5 (107)
Female	38.5 (74)	39.6 (70)
<b>Presence of <i>S. aureus</i> at baseline</b>		
Yes	92.2 (177)	100 (177)
No	7.8 (15)	
<b>Prior antibiotic treatment</b>		
Yes	43.2 (83)	42.9 (76)
No	56.8 (109)	57.1 (101)
<b>Infection type</b>		
Cellulitis	18.8 (36)	18.1 (32)
Major abscess	44.3 (85)	42.9 (76)
Other deep soft tissue	19.8 (38)	20.9 (37)
Surgical wound	7.8 (15)	7.9 (14)
Traumatic wound	9.4 (18)	10.2 (18)
<b>Involvement of infection at baseline</b>		
Deep	89.6 (172)	89.8 (159)
Superficial	10.4 (20)	10.2 (18)
<b>Presence of diabetes mellitus</b>		
Yes	32.3 (62)	30.5 (54)
No	67.7 (130)	69.5 (123)
<b>Presence of vascular disease</b>		
Yes	13.0 (25)	13.0 (23)
No	87.0 (167)	87.0 (154)
<b>Presence of polymicrobial infection</b>		
Yes	8.3 (16)	7.9 (14)
No	91.7 (176)	92.1 (163)

- ### Efficacy Endpoints

Efficacy endpoints included clinical and microbiological responses assessed at the End-of-Therapy (EOT; within 3 days of completion of therapy) and Test-of-Cure (TOC; Day 14 ± 2 days) visits, lesion size reduction from baseline in area of the infection assessed on Days 4 and 8, and at EOT and TOC (**Table 3.2.2-2**).

**Table 3.2.2-2.** Dichotomous and Continuous Endpoints Included in the PK-PD Analysis

<b>Efficacy endpoint category</b>	<b>Efficacy endpoint</b>
Dichotomous	Clinical response at EOT and TOC  Microbiological response at EOT and TOC  Cessation of spread and $\geq 10, 20, 30,$ and $50\%$ reduction from baseline in the area of infection on Days 4 and 8
Continuous	Percent change from baseline in the area of infection on Days 4 and 8

- **Pharmacokinetic-Pharmacodynamic Analyses**

Univariable Analysis

Univariable relationships for dichotomous efficacy endpoints were examined using Chi square or Fisher's exact tests for categorical independent variables and logistic regression for continuous independent variables. Univariable relationships for continuous efficacy endpoints were evaluated using linear regression. AUC from time of dose to 120 hours ( $AUC_{0-120}$ ) was estimated for each patient using the population PK model, and  $AUC_{avg}$  was calculated as  $AUC_{0-120}$  divided by 5 days.

Independent variables:  $AUC_{avg}$  ( $AUC_{0-120}/5$ ); baseline MIC;  $AUC_{avg}/MIC$ ; patient demographic and disease-related characteristics, as shown in **Table 3.2.2-3**.

**Table 3.2.2-3.** List of Independent Variables Evaluated

<b>Demographic</b>	<b>Disease-related or underlying comorbidities</b>
Age (yrs)	Area of infection at baseline ( $cm^2$ )
Albumin (g/dL)	Involvement of infection at baseline
Body mass index (BMI) ( $kg/m^2$ )	Presence of diabetes mellitus
CLcr ( $mL/min/1.73 m^2$ )	Presence of polymicrobial infection
Race/Ethnicity	Presence of <i>S. aureus</i> at baseline
Sex	Presence of vascular disease
Weight (kg)	Infection type (traumatic wound, surgical wound, other deep soft tissue infection, major abscess, cellulitis) Prior antibiotic treatment

Each continuous independent variable was divided into quartiles, as a two-group categorical variable to avoid concerns about non-linearity, and also a three-group categorical variable to further characterize nonlinearity or non-monotonicity. The thresholds used to define the categorical variables were those that were optimally-determined for the given efficacy endpoint. Two-group independent variables were constructed by using the resulting split of a classification tree for a given dichotomous efficacy endpoint and the resulting split of a regression tree for a continuous efficacy endpoint. Three-group independent variables were constructed by determining a pair of cutoff values that minimized the likelihood ratio P-value using either

logistic regression for a dichotomous efficacy endpoint or linear regression for a continuous efficacy endpoint.

### Multivariable analysis

Multivariable analysis were considered for each efficacy endpoint if a statistically significant ( $p < 0.05$ ) or borderline-significant ( $p = 0.05$  to  $0.1$ ) biologically plausible univariable relationship between  $AUC_{avg}$ , MIC, or  $AUC_{avg}/MIC$  and the given efficacy endpoint was identified. A biologically plausible relationship was one in which the efficacy endpoint was improved at high drug exposures or low MIC values.

- **Selection of in vitro susceptibility test interpretive criteria for dalbavancin against *Staphylococcus aureus***

Plasma concentration time profiles of 5,000 simulated patients were generated following dalbavancin 1000 mg (or 750 mg for severe renal impairment patients) on Day 1, by using the developed population PK model and with covariates distributions based on data from patients with ABSSSI.  $AUC_{avg}/MIC$  was then calculated for fixed MIC values of 0.03, 0.06, 0.12, and 0.25 mg/L. Using parameter estimates from univariable PK-PD models for efficacy from patients with *S. aureus*, model-predicted percent probabilities of response by fixed MIC values were determined for each simulated patient. The mean model-predicted percent probabilities of response for fixed MIC values were then determined by averaging across all simulated patients.

### 3.2.3 Results

A total of 192 patients who received dalbavancin 1000 mg on Day 1 and 500 mg on Day 8 and had PK data were included in the EOT and/or TOC ME populations. Greater than 85% of these patients were evaluable for clinical or microbiological response at EOT or TOC and efficacy endpoints on Day 4 or 8.

**Table 3.2.3-1** presents percentages of clinical and microbiological responses at EOT and TOC, while **Table 3.2.2-2** shows percentages of patients achieving area of infection endpoints on Days 4 and 8 for all patients and patients with *S. aureus*.

**Table 3.2.3-1.** Clinical and microbiological response at EOT and TOC

Analysis population	Visit	Clinical response		Microbiological response	
		Success % (n/N)	Failure % (n/N)	Success % (n/N)	Failure % (n/N)
All patients	EOT	95.6 (173/181)	4.4 (8/181)	88.9 (160/180)	11.1 (20/180)
	TOC	92.6 (162/175)	7.4 (13/175)	91.4 (160/175)	8.6 (15/175)
Patients with <i>S. aureus</i>	EOT	95.8 (160/167)	4.2 (7/167)	88.6 (147/166)	11.4 (19/166)
	TOC	92.6 (150/162)	7.4 (12/162)	91.4 (148/162)	8.6 (14/162)

**Table 3.2.3-2.** Percentage of patients achieving area of infection endpoints on Days 4 and 8 using data from all patient and patients with *S. aureus*

Analysis population	Study day	Area of infection endpoints				
		Cessation of spread % (n/N)	Percent reduction from baseline (n/N)			
			≥ 10%	≥ 20%	≥ 30%	≥ 50%
All patients	4	97.3 (180/185)	88.6 (164/185)	84.3 (156/185)	78.4 (145/185)	62.7 (116/185)
	8	97.2 (175/180)	95.0 (171/180)	94.4 (170/180)	91.7 (165/180)	86.7 (156/180)
Patients with <i>S. aureus</i>	4	97.1 (165/170)	87.6 (149/170)	82.9 (141/170)	76.5 (130/170)	62.9 (107/170)
	8	97.0 (161/166)	94.6 (157/166)	94.0 (156/166)	91.0 (151/166)	85.5 (142/166)

Preclinical data demonstrated that AUC/MIC is predictive of dalbavancin efficacy. Similarly, univariable relationships were identified between dichotomous efficacy endpoint and AUC<sub>avg</sub>/MIC as a two-group variable. **Table 3.2.3-3** summarizes these univariable relationships for selected efficacy endpoints. The univariable relationship between dichotomous efficacy endpoints and AUC<sub>avg</sub> was identified with similar statistical significance. When evaluating MIC as an independent variable, no meaningful trend was revealed between dichotomous efficacy endpoint and MIC.

The Sponsor indicated that results for the univariable PK-PD analyses for percent change in the area of infection on Days 4 or 8 (as continuous variables) were not more informative than those for dichotomous endpoints based on ≥ 10 to 30% change in the area of infection on Days 4 or 8. The general trends of univariable relationships between area of infection endpoints on Day 8 and AUC<sub>avg</sub>/MIC were consistent with the results shown in the efficacy endpoint on Day 4. However, the Sponsor noted that the Day 8 results had more patients achieved the lesion size reduction endpoints and thus reduced the likelihood of identifying univariable relationships for the endpoints.

**Table 3.2.3-3.** Summary of univariable relationships between dichotomous efficacy endpoints and AUC<sub>avg</sub>/MIC

Efficacy endpoint	All patients				Patients with <i>S. aureus</i>			
	AUC <sub>avg</sub> :MIC ratio threshold	Patients < or ≥ threshold achieving efficacy endpoint		P-value	AUC <sub>avg</sub> :MIC ratio threshold	Patients < or ≥ threshold achieving efficacy endpoint		P-value
		< threshold % (n/N)	≥ threshold % (n/N)			< threshold % (n/N)	≥ threshold % (n/N)	
Clinical success at EOT	16,038	90.6 (29/32)	96.6 (144/149)	0.15	21,267	93.9 (107/114)	100 (53/53)	0.10
Microbiological success at EOT	14,472	66.7 (10/15)	90.9 (150/165)	0.015	14,472	64.3 (9/14)	90.8 (138/152)	0.012
Clinical success at TOC	21,267	89.3 (100/112)	98.4 (62/63)	0.034	21,267	89.1 (98/110)	100 (52/52)	0.01
Microbiological success at TOC	13,658	75.0 (9/12)	92.6 (151/163)	0.07	13,658	75.0 (9/12)	92.7 (139/150)	0.07
≥ 10% reduction from baseline in the area of infection on Day 4	16,096	77.1 (27/35)	91.3 (137/150)	0.033	16,096	75.8 (25/33)	90.5 (124/137)	0.035
≥ 20% reduction from baseline in the area of infection on Day 4	13,396	50.0 (5/10)	86.3 (151/175)	0.01	14,320	53.8 (7/13)	85.4 (134/157)	0.011
≥ 30% reduction from baseline in the area of infection on Day 4	14,320	42.9 (6/14)	81.3 (139/171)	0.003	14,320	38.5 (5/13)	79.6 (125/157)	0.003

The final multivariable models were developed based on data from all patients and patients with *S. aureus* for EOT and TOC and Day 4 dichotomous area of infection endpoints. The results demonstrated retention of age, AUC<sub>avg</sub>/MIC, BMI, CRCL, diabetes, or infection type in one or more of the final models. A summary of the multivariable models with regard to whether AUC<sub>avg</sub>/MIC was retained and the corresponding p-value is provided in Table 3.2.3-4.

**Table 3.2.3-4.** Summary of multivariable models containing AUC<sub>avg</sub>/MIC

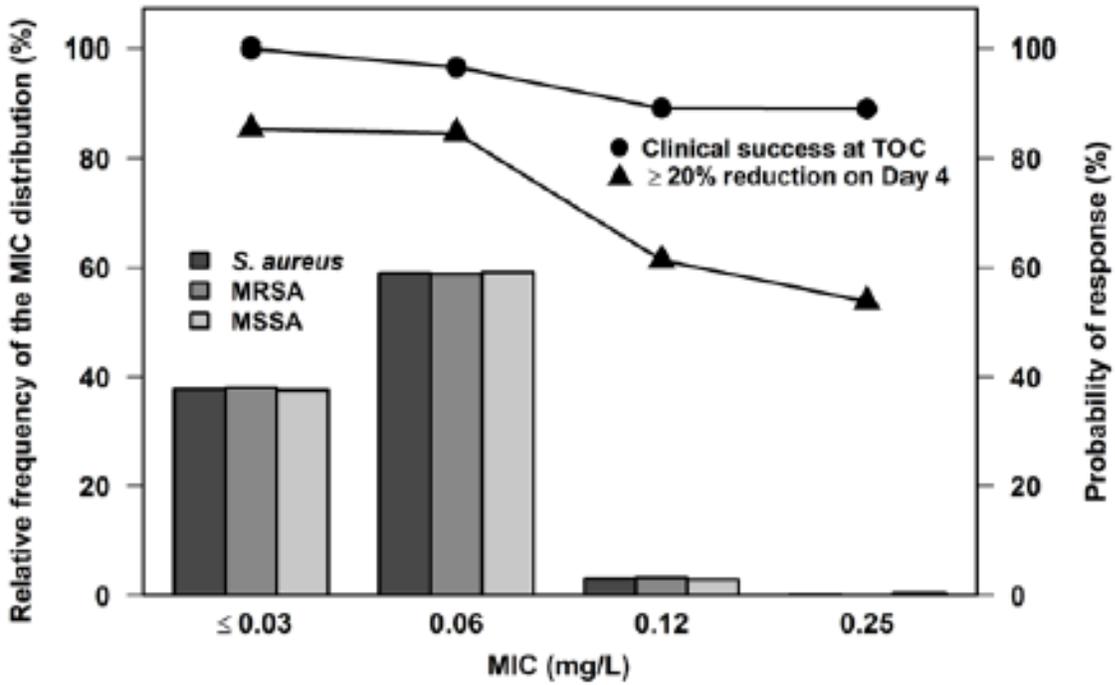
Efficacy endpoint	All patients		<i>S. aureus</i> patients	
	Retention of AUC <sub>avg</sub> :MIC ratio <sup>a</sup>	P-value	Retention of AUC <sub>avg</sub> :MIC ratio <sup>a</sup>	P-value
Clinical response at TOC	No	0.073	Yes	0.020
Microbiological response at EOT	Yes	0.060	Yes	0.052
Microbiological success at TOC	Yes	0.036	No	0.081
≥ 10% reduction from baseline in the area of infection on Day 4	No	0.66	No	0.53
≥ 20% reduction from baseline in the area of infection on Day 4	No	0.35	No	0.12
≥ 30% reduction from baseline in the area of infection on Day 4	No	0.067	No	0.052

a. "Yes" signifies that AUC<sub>avg</sub>:MIC ratio was retained in the final multivariable through the step-wise procedure. "No" signifies that AUC<sub>avg</sub>:MIC ratio was not in the final model. The p-values show the level of significance if AUC<sub>avg</sub>:MIC ratio was added to the final model.

In the Sponsor's multivariable analysis, the results demonstrated retention of age,  $AUC_{avg}/MIC$ , BMI, CLcr, diabetes, or infection type in one or more of the final models. General trends were observed when assessing relationships between independent variables (**Table 3.2.2-3**) and clinical outcomes. The most significant trend of each variable is summarized with p value and associated clinical outcome, as follows. Older patients (> 56 years) had a lower percentage of successful responses than those who were younger ( $p=0.043$  microbiological success at EOT from patients with *S. aureus*). Patients with  $AUC_{avg}/MIC$  equal and higher than 21267 had a higher percentage of successful responses than those with  $AUC_{avg}/MIC$  lower ( $p=0.02$ , clinical success at TOC for patient with *S. aureus*). Patients with BMI lower than  $27.8 \text{ kg/m}^2$  had a higher percentage of successful responses than those with higher BMI ( $p=0.005$ , clinical success at TOC for patient with *S. aureus*). Patients with CRCL lower than  $177 \text{ mL/min/1.73m}^2$  had a higher percentage of successful responses than those with higher CRCL ( $p=0.009$ , microbiological success at EOT). Patients with diabetes had a lower percentage of successful responses than those who were not diabetic ( $p=0.006$ ,  $\geq 20\%$  reduction in area of infection on Day 4). Patients with cellulitis or soft tissue infections had a higher percentage of successful response than those with major abscess or surgical or traumatic wound infections ( $p=0.0003$ ,  $\geq 10\%$  reduction in area of infection on Day 4).

The parameter estimates from univariable relationships shown above were used to determine model-predicted percent probabilities of response for each efficacy endpoint by MICs. The mean percent probability of a successful clinical response at TOC exceeded or approached 90% up to an MIC value of 0.25 mg/L. The mean percent probability of  $\geq 20\%$  reduction from baseline in the area of infection on Day 4 was 84.6% at an MIC of 0.06 mg/L, as shown in **Table 3.2.3-5**. **Figure 3.2.3-1** depicts the mean of predicted probabilities of response overlaid with MIC distribution of *S. aureus*, MRSA, and MSSA.

**Figure 3.2.3-1.** Mean model-predicted percent probabilities of response by MIC overlaid over MIC distributions for *S. aureus*



**Table 3.2.3-4.** Mean Model Predicted Probabilities of Response by MIC Value for Dalbavancin against *S. aureus*

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

### 3.2.4 Highlights of the Sponsor's Conclusions

- Results of univariable analyses of Study VER001-9 demonstrated significant PK-PD relationships for EOT, TOC, and area of infection efficacy endpoints:
  1. AUC<sub>avg</sub>/MIC ratios ranging from 13,658 to 21,267 were associated with a higher percentage of patients achieving clinical or microbiological success at EOT or TOC.
  2. AUC<sub>avg</sub>/MIC ratios ranging from 13,396 to 16,096 were significantly associated with a higher percentage of patients achieving  $\geq 10$ , 20, and 30% reduction from baseline in the area of infection on Day 4.
- Multivariable analyses for EOT or TOC efficacy endpoints demonstrated retention of AUC<sub>avg</sub>/MIC as a significant variable when evaluated with other independent variables for the majority of the models constructed.
- Using the PK-PD relationship for clinical response at TOC based on data from patients with *S. aureus* at baseline, the mean model-predicted percent probability of a successful clinical response exceeded or approached 90% up to an MIC value of 0.25 mg/L.
- Given that the percentage of patients achieving the AUC<sub>avg</sub>/MIC thresholds was higher compared to those not achieving these thresholds for most of the efficacy endpoints evaluated, results of these analyses provide support for the dalbavancin dosing regimen of 1000 mg IV dose on Day 1 followed by a 500 mg IV dose on Day 8. Additionally, these data provide support for establishing in vitro interpretive criteria for dalbavancin against *S. aureus*.

#### **Overall Reviewer's Comment for PK-PD Analysis:**

*In the sponsor's analysis AUC/MIC was best correlated with dichotomous efficacy endpoints, compared to AUC/MIC as a continuous variable or AUC or MIC as independent continuous or dichotomous variables. This finding is consistent to the results from the preclinical studies. The Sponsor proposed to determine the dalbavancin breakpoint using the PK-PD relationship that was developed based on clinical success at TOC. This strategy is an ongoing discussion topic within the infectious diseases community and the Agency, and is one of the approaches for setting breakpoints. However, in the case of dalbavancin, there are several concerns associated with the limited MIC distribution in the clinical studies. In addition, the selected efficacy endpoint is a concern, which may also confound identification of an appropriate dalbavancin breakpoint. Further discussion of these limitations is as follows:*

- a) *MIC values in a majority of the patients (over 96%) in the clinical studies were 0.06 mg/L. Likewise, the occurrences of *S. aureus* isolates with MICs of 0.12 and 0.25 mg/L were 3.1% and 0.019% of the total population, respectively. Thus, the calculated mean probability of achieving endpoints at MIC of 0.25 mg/L is an extrapolation of the existing information and may not accurately reflect response rates with increasing MIC values.*

b) *The Sponsor proposed a dalbavancin breakpoint using the PK-PD relationship based on the efficacy data of clinical success at TOC. However, this PK-PD relationship should be interpreted with caution due to the small percentage of clinical failures (<7.5% failure). The Sponsor's simulations used the observed response rate in subjects with  $AUC/MIC$  values above and below the threshold value to derive the mean probability of success for each MIC. In detail, this PK-PD relationship corresponded to 100% response above 21,267 and 89.1% below  $AUC_{avg}/MIC$  of 21,267 in patients with *S. aureus*. Simulations based on these percentages would result in a minimum predicted response rate of 89.1% if all subjects had an  $AUC/MIC$  below 21,267, which is the simulation result provided by the sponsor for an MIC of 0.25 mg/L. As such, it may not be appropriate to interpret the simulation results of the clinical success at TOC as supportive of an MIC of 0.25 mg/L. PK-PD analyses based on other endpoints involving a dichotomous endpoint will also encounter similar issues, with the predicted response rate bounded between the response rate observed in the group of subjects above and below the identified threshold value.*

*To assist in selection a breakpoint for dalbavancin based on the efficacy measures, the reviewer recommends identifying the inflection point in the univariable PK-PD analysis, defined as the MIC value corresponding to the largest decreasing transit between consecutive MIC values. Selection of such a value would be similar to the inflection point from a sigmoidal PK-PD relationship for a continuous variable. Also, instead of clinical success at TOC, using efficacy endpoints of percentage reductions in the area of infection on Day 4 may assist in visualizing this transit since the separation between the dichotomous groups was more pronounced for these endpoints. As shown in the reviewer's analysis (refer to 4.3), the dalbavancin break point determined using lesion size reduction efficacy endpoints on Day 4 is 0.06 mg/L. In addition, the multivariable analysis results indicated that age,  $AUC_{avg}/MIC$ , BMI, CRCL, diabetes, or infection type were associated with clinical success rate. However, it should be noted that the above-mentioned trends were not observed consistently across all clinical outcomes. For example, the trend of older people (> 56 years) having a lower percentage of successful responses than younger ones was only observed for the clinical outcome of microbiological success at EOT. The multivariable results also found opposite directions between  $AUC_{avg}/MIC$  or CRCL and clinical response rate, which might be inherently related. However, the Sponsor further stated that the effect of CRCL on the given efficacy endpoint was not simply explained by that of  $AUC_{avg}/MIC$  based on modeling results. This may suggest that additional confounding factors influence the relationship between  $AUC_{avg}/MIC$  and clinical outcomes but those could not be identified based on these data. Thus, caution is warranted when interpreting the observed trends from the multivariable analysis results, due to lack of consistency across clinical endpoints.*

## 4 Reviewer's Analysis

### 4.1 Objectives

The objectives of the analysis are:

1. To evaluate covariate model proposed in the Sponsor's population PK analysis.
2. To evaluate *in vitro* susceptibility test interpretive criteria for dalbavancin against *staphylococcus aureus* by using the PK-PD relationships developed from all available efficacy endpoints in the ABSSSI patients with *S. aureus* infection.

### 4.2 Methods

#### 4.2.1 Evaluation of *In Vitro* Susceptibility Test Interpretive Criteria (Break Point) for Dalbavancin against *Staphylococcus Aureus*

First, a repetition analysis was performed to confirm the parameters estimated in the Sponsor's PK-PD analysis. The  $AUC_{avg}/MIC$  was used as the independent variable that is considered best correlated with selected efficacy endpoints in the PK-PD analysis. The reviewer's analysis evaluated the suitability of PK-PD relationships for all selected efficacy endpoints in determination of dalbavancin breakpoint against *S. aureus*. The developed PK-PD relationships are subsequently used for calculation of probability of responses at each MIC category. The same dataset of PK, efficacy, and simulated exposure were included in the PopPK and PK-PD analysis. Logistic regression, probability calculation, and plotting were performed using R.

### 4.3 Results

#### 4.3.1 Evaluation of *In Vitro* Susceptibility Test Interpretive Criteria for Dalbavancin (Breakpoint) Using Exposure-Response Relationships

As presented above, the Sponsor used the PK-PD relationship for clinical success at TOC to inform dalbavancin breakpoint against *S. aureus*. Based on this endpoint, a breakpoint of 0.25 mg/L against *S. aureus* was proposed in the current NDA submission. By reviewing the results of PK-PD analysis, the univariable PK-PD relationship for clinical success at TOC showed a high percentage of patients achieving efficacy endpoint (89.1%) who did not achieve the  $AUC_{avg}/MIC$  threshold.

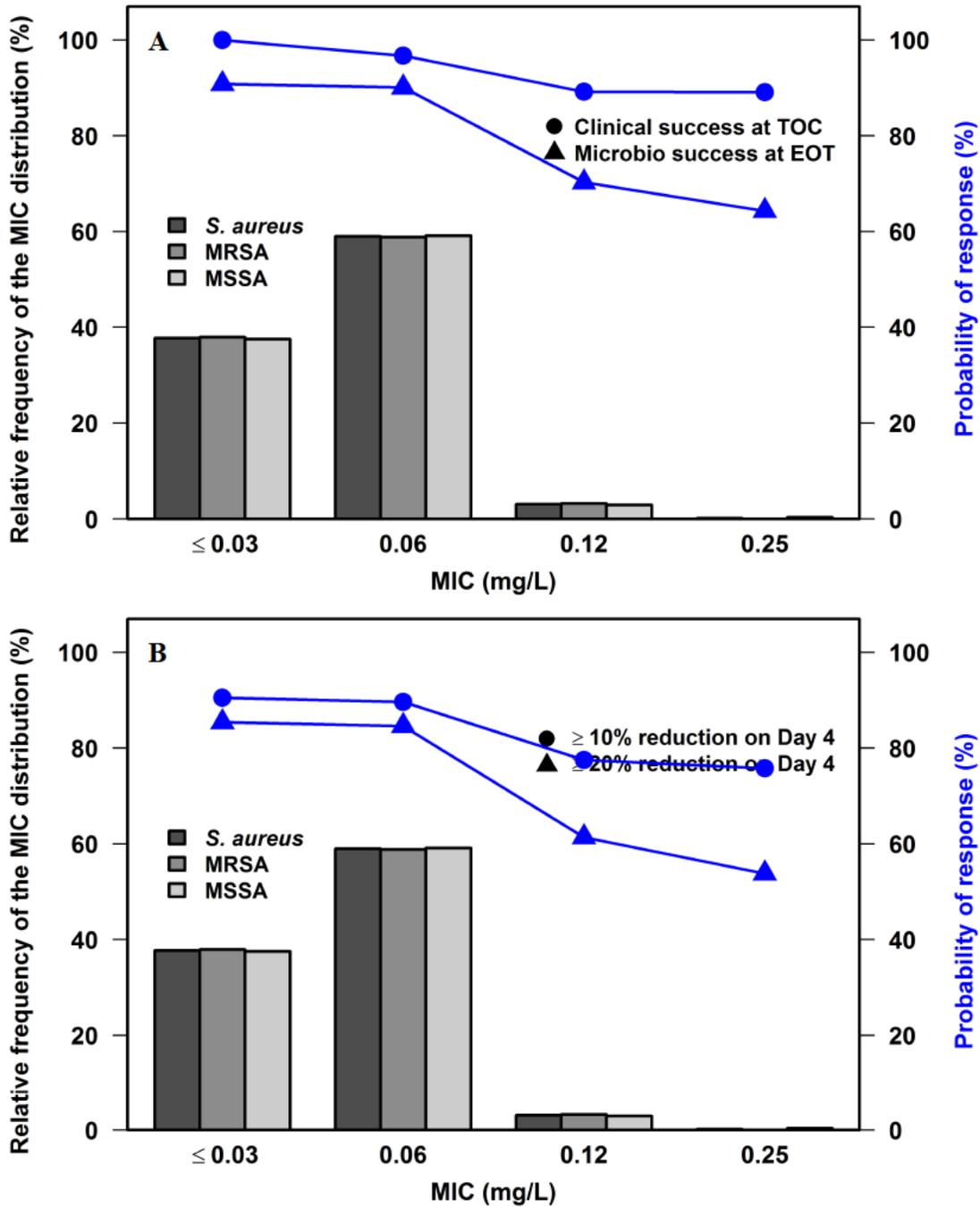
However, the developed PK-PD relationship for the clinical success at TOC may be not robust enough to inform the breakpoint determination based on the number of subjects with MIC values  $>0.06$  mg/L included in the analysis, although this relationship is statically significant. The occurrence of pathogens with MIC of  $\leq 0.06$  mg/L was over 96.7 % in the MIC distribution for *S. aureus* included in the breakpoint determination. In contrast, less than 0.2% of isolates had MIC of 0.25 mg/L, which may bias predictions of the probability of achieving clinical success at TOC for patients with the isolate of 0.25 mg/L MIC. Furthermore, the current FDA guidance for ABSSSI treatment recommends that primary efficacy endpoints should be  $\geq 20\%$  reduction in the lesion size at 48 to 72 hours compared to baseline. Thus, it is necessary to evaluate clinical responses at early time points and also assess the suitability of these early efficacy endpoints in determination of dalbavancin breakpoints in comparison with the already mentioned clinical and microbial success endpoints.

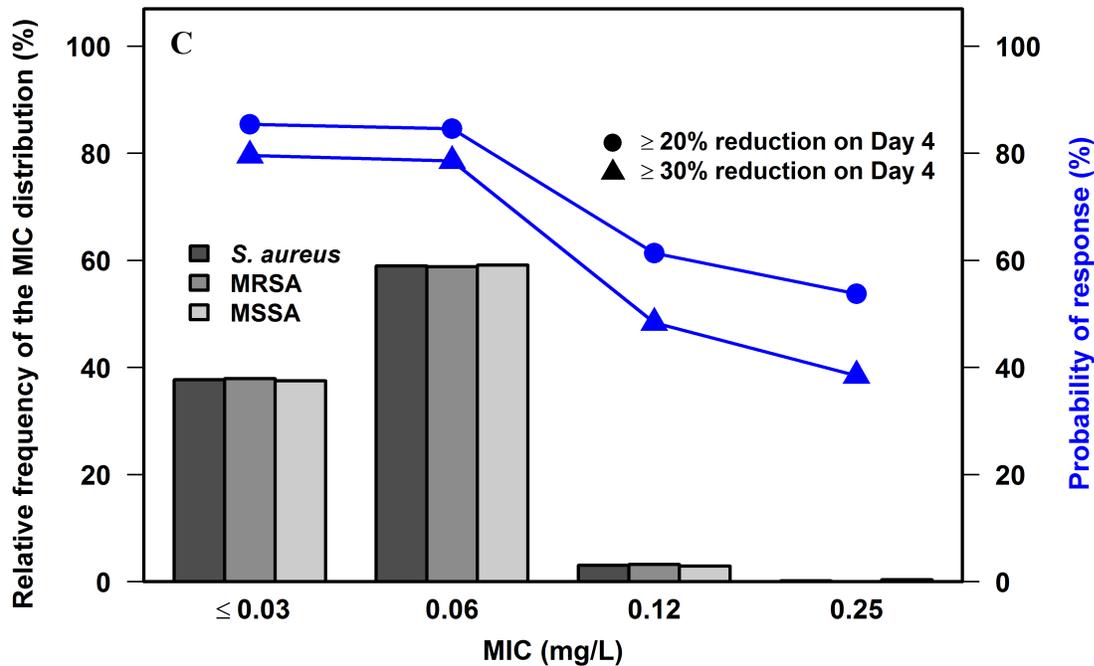
In the current analysis performed by the reviewer, the predicted PK-PD relationships for all selected efficacy endpoints (clinical success TOC, microbial success EOT, and legions size changes at day 4) are used for the derivation of probabilities of responses at each MIC category. The predicted PK-PD relationships based on clinical success at EOT and microbiological success at TOC are excluded in the analysis, since these univariable relationships were not statistically significant (*refer to 3.2.3 Table 9*). **Table 4.3.1-1** presents mean model predicted probabilities of response by MIC values for dalbavancin against *S. aureus*, based on each of the five selected efficacy endpoints. **Figure 4.3.1-1** graphically depicts the probabilities of these efficacy endpoints overlaid with the MIC distribution for *S. aureus* and the subsets of MRSA and MSSA isolates. Note that few subjects had isolates with MIC >0.12 mg/L

**Table 4.3.1-1.** Mean model predicted probabilities of response by MIC values for dalbavancin against *S. aureus*.

MIC	Mean model-predicted probability of responses				
	Clinical success at TOC	Micro success at EOT	≥ 10% reduction from baseline in the area of infection on Day 4	≥ 20% reduction from baseline in the area of infection on Day 4	≥ 30% reduction from baseline in the area of infection on Day 4
<b>0.03</b>	100	90.8	90.5	85.4	79.6
<b>0.06</b>	96.7	90.1	89.6	84.6	78.6
<b>0.12</b>	89.2	70.3	77.5	61.4	48.4
<b>0.25</b>	89.1	64.3	75.8	53.8	38.5

**Figure 4.3.1-1.** Probabilities of efficacy endpoints overlaid with the MIC distribution for *S. aureus* and the subsets of MRSA and MSSA isolates, including Clinical success at TOC and Microbiological success at EOT (Panel A), 10%, 20%, and 30% reduction in size of lesion area on Day 4 (Panels B and C).





Similar patterns were observed in the predicted mean probabilities for all three efficacy endpoints based on lesion size reduction ( $\geq 10\%$ ,  $\geq 20\%$ , and  $\geq 30\%$ ) on Day 4 (Figure 4.3.1-1B and C), in which the most substantial decrease was observed when transitioning above an MIC of 0.06 mg/L. The reason for this observation is based on the dichotomous AUC/MIC threshold used by the Sponsor for conducting PK-PD simulations which results in predicted response rate bounded between the response rates observed in the group of subjects above and below the identified threshold value. *A benefit of using lesion size reduction in this analysis rather than clinical success is that the drop-off between maximum and minimum response is better visualized using percentage reductions in the area of infection on Day 4 given the currently available trial data.*

Based on the above findings, the reviewer concluded that a susceptibility breakpoint of dalbavancin against *S. aureus* can be sufficiently determined by the PK-PD relationship for  $\geq 10\%$  or 20% reduction from baseline in the area of infection on Day 4 and a breakpoint of 0.06 mg/L for *S. aureus* is more appropriate, in contrast to 0.25 mg/L as proposed by the Sponsor. However, it should be noted that the determination of breakpoints involves multiple disciplines providing clinical and microbial observations in addition to the above PK-PD observations. The ultimate determination of the dalbavancin breakpoint will depend on the totality of information provided by each discipline and continues to be assessed as of the completion of this review.

5 **References:**

1. Wang DD, Zhang S. Standardized visual predictive check versus visual predictive check for model evaluation. *J Clin Pharmacol*. 2012 Jan;52(1):39-54.

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YANG HE  
03/04/2014

JEFFRY FLORIAN  
03/04/2014

KIMBERLY L BERGMAN  
03/04/2014

<b>BIOPHARMACEUTICS REVIEW</b>			
<b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 21-883	<b>Reviewer:</b>	
<b>Division:</b>	DAIP	Houda Mahayni, Ph.D.	
<b>Applicant:</b>	Durata Therapeutics, Inc.	<b>Team Leader:</b>	
<b>Trade Name:</b>	Dalvance™ (proposed)	Angelica Dorantes, Ph.D.	
<b>Generic Name:</b>	Dalvavancin (DUR001)	<b>Acting Supervisor:</b>	
<b>Indication:</b>	Treatment of adult patients with Acute Bacterial Skin and Skin Structure Infections (abSSSI) caused by susceptible strains of Gram-positive bacteria	<b>Date Assigned:</b>	September 30, 2013
<b>Formulation/strength</b>	Powder for Injection/500 mg	<b>Date of Review:</b>	February 27, 2014
<b>Route of Administration</b>	Intravenous		
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<b>Submission Date:</b>		<b>Date of Consult</b>	<b>PDUFA DATE</b>
September 26, 2013		September 30, 2013	May 26, 2014
<b>Type of Submission:</b>	505 (b) (1)		
<b>Key review points</b>	Evaluation of the data supporting the bridging across the phases of development for the proposed product		

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- p. Do the proposed or reference product contain excipients that can affect the disposition and/or distribution of the drug?*
- q. What is the difference in pH, administered volume, and osmolarity of the proposed and the reference drug product?*
- r. Are the CFR requirements for granting a biowaiver met? If not, are the provided justification and supportive data appropriate?*
- s. Is the overall information supporting the biowaiver request acceptable?*
- t. Is the biowaiver granted?*

## EXECUTIVE SUMMARY

**Background:** Original NDA 21883 for Dalbavancin was submitted in accordance with the regulations set forth in section 505 (b) (1) of the FDC Act. This NDA was initially submitted by Vicuron Pharmaceuticals, Inc. (Vicuron), on December 21, 2004, and withdrawn by Pfizer, Inc. (Pfizer), on September 15, 2008. Durata Therapeutics Inc. (Durata) assumed responsibility of this NDA 21-883 on December 11, 2009.

During the course of earlier clinical development in support of the 2004 NDA submission, three product strengths were produced utilizing two different formulations, but the manufacturing process remained essentially the same. The initial clinical formulation was a 200 mg/vial strength that was developed and manufactured at the original clinical manufacturing site, (b) (4). During the course of development at (b) (4) 250 mg/vial strength was also developed and both strengths were used in Vicuron-sponsored Phase 2/3 studies. Concurrent with the initial Phase 3 studies, 500 mg/vial strength was developed and produced at (b) (4). The 500 mg product was then transferred to the current manufacturing site, (b) (4).

In the previous NDA submission of 2004, Phase 3 clinical studies VER001-8 and VER001-9 used both 200 mg and 250 mg vials, whereas the Phase 3 study VER001-16 used only 250 mg vials. All other Phase 1 and 2 clinical studies used the 200 mg vials.

Although the pharmacokinetics of dalbavancin were characterized in the previous submission following administration of the currently proposed dosage regimen (1000 mg on day 1 and 500 mg on day 8) in Study VER001-12 (hepatic impairment study), the 200 mg formulation was used not the proposed 500 mg formulation (See in DAARTS the Clinical Pharmacology review by Dr. Charles Bonapace dated September 20, 2005).

**Submission:** Dalbavancin (DUR001) for injection is a semisynthetic lipoglycopeptide antibiotic. It was developed as an IV treatment for serious bacterial infections, in particular those caused by staphylococci and streptococci including methicillin-resistant staphylococci. The proposed indication for dalbavancin is for the treatment of adult patients with Acute Bacterial Skin and Skin Structure Infections (abSSSI). The recommended dosing regimen is 1000 mg of IV dalbavancin on the first day of therapy (Day 1), followed a week later (Day 8) by 500 mg of IV dalbavancin. Both doses of dalbavancin are infused over a 30-minute period. In the present NDA submission, the Applicant plans to market only the 500 mg dosage strength.

The proposed commercial formulation is a sterile lyophilized solid, which is reconstituted at the time of use. The product contains dalbavancin hydrochloride equivalent to 500 mg of dalbavancin free base per vial as the active ingredient. Dalbavancin drug product requires two preparatory steps prior to administration: reconstitution with sterile water for injection to form the reconstituted product and the reconstituted product is then diluted with a suitable infusion solution prior to infusion.

**Review:** The Biopharmaceutics review focused on the evaluation of the data supporting the bridging across the phases of development for the proposed product.

## **I) BIOPHARMACEUTICS FINDINGS**

Dalbavancin drug substance is an amorphous solid. It is freely soluble in water. The proposed commercial formulation is a sterile lyophilized powder, which is reconstituted at the time of use. The product contains dalbavancin hydrochloride equivalent to 500 mg of dalbavancin free base per vial as the active ingredient. Dalbavancin drug product requires two preparatory steps prior to administration: reconstitution with sterile water for injection to form the reconstituted product; and the reconstituted product is then diluted with a suitable infusion solution prior to infusion.

Although during the course of development three dosage strengths (200 mg, 250 mg, and 500 mg) were produced utilizing different manufacturing sites, different formulations, and essentially the same manufacturing process, only the 500 mg strength is proposed for marketing and it is the strength that was used in Phase 3 studies sponsored by Durata in the current submission.

Bridging across the phases of development is found acceptable, as the proposed commercial process, formulation, and manufacturing site are essentially the same as used for manufacture of the phase 3 clinical trial supplies. Durata clinical trials, including two Phase 3 studies (DUR001-301 and 302), utilized the proposed 500 mg/vial product. Also, the Applicant performed a pilot study to determine the plasma concentrations following administration of Dalbavancin 1500 mg by intravenous infusion in healthy volunteers (DUR001-101). This study utilized the proposed 500 mg strength. Hence, no biowaiver for BA studies is needed for this product.

## **II) RECOMMENDATION**

The ONDQA-Biopharmaceutics team reviewed NDA 21883 for Dalvance™ (Dalbavancin) Powder for Injection, 500 mg, and found appropriate bridging across the phases of development for the proposed product.

From the Biopharmaceutics perspective, NDA 21883 for Dalvance™ (Dalbavancin) Powder for Injection, 500 mg is recommended for approval.

**Houda Mahayni, Ph. D.**  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Angelica Dorantes, Ph.D.**  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

*cc: DARRTS/Lostritto*

### III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

#### A) GENERAL ATTRIBUTES

- a. *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility)?*

Dalbavancin drug substance is an amorphous solid. It is freely soluble in water and more soluble in acidic aqueous solutions below pH (b) (4). The solubility of dalbavancin drug substance at ambient temperatures is provided in Table 1.

**Table 1: Dalbavancin Solubility in Aqueous Buffers**

pH	Buffer	Solubility (µg/mL)
(b) (4)		

- b. *What is the route of administration? How is the product being administered?*

The proposed product is an injectable to be administered intravenously. The recommended dosing regimen is 1000 mg of IV dalbavancin on the first day of therapy (Day 1), followed a week later (Day 8) by 500 mg of IV dalbavancin. Both doses of dalbavancin are infused over a 30-minute period.

- c. *Does the drug product include a delivery device?*

No.

#### B) DRUG PRODUCT FORMULATION

- d. *What is the formulation?*

The proposed commercial formulation is a sterile lyophilized powder, which is reconstituted at the time of use. The product contains dalbavancin hydrochloride equivalent to 500 mg of dalbavancin free base per vial as the active ingredient. Dalbavancin drug product requires two preparatory steps prior to administration: reconstitution with sterile water for injection to form the reconstituted product (the reconstituted product contains 20 mg/mL dalbavancin, (b) (4) mannitol and (b) (4) lactose monohydrate); and the reconstituted product is then diluted with a suitable infusion solution to a concentration between 1 and 5 mg/mL prior to infusion.

The quantitative composition of the proposed commercial product is provided in Table 2.

**Table 2: Composition of Dalbavancin for Injection, 500 mg Vials**

Ingredient	Composition of Fill Solution	Quantity per Vial <sup>a</sup>	Function	Reference to Standards
Dalbavancin	0.050 g/mL <sup>b</sup>	(b) (4)	Active Ingredient	N/A
Mannitol				(b) (4)
Lactose Monohydrate				(b) (4)
Sodium hydroxide <sup>c</sup>				(b) (4)
Hydrochloric acid <sup>e</sup>				(b) (4)
				(b) (4)
<b>Total Weight</b>		<b>772.6 mg</b>		(b) (4)

<sup>b</sup> Anhydrous dalbavancin free base.

**e. What are the highlights of the drug product formulation development?**

During the course of development three product strengths were produced utilizing two different formulations, but the manufacturing process remained essentially the same. The initial clinical formulation was a 200 mg/vial strength that was developed and manufactured at the original clinical manufacturing site, (b) (4)

During the course of development at (b) (4) 250 mg/vial strength was also developed and both strengths were used in Vicuron-sponsored Phase 2/3 studies. Concurrent with the initial Phase 3 studies, a 500 mg product was developed and produced at (b) (4). The 500 mg product was then transferred to the current manufacturing site, (b) (4). The proposed 500 mg product was used in Phase 3 studies sponsored by Durata.

**Reviewer's Note:**

The Applicant performed two Phase 3 studies with the proposed 500 mg formulation. Therefore, no BE studies are required to link the proposed formulation to earlier formulations studied during development. And, the Applicant performed a pilot study to determine the plasma concentrations following administration of Dalbavancin 1500 mg by intravenous infusion in health volunteers (DUR001-101). This study utilized the proposed 500 mg strength. Hence, no biowaiver for BA studies is needed for this product.

### C) SUPPORTIVE INFORMATION

- f. *What data are available to support the approval of the proposed product?***  
Durata clinical trials, including two Phase 3 studies (DUR001-301 and DUR001-302), utilized the proposed 500 mg/vial product and will be the basis on which to determine the safety and efficacy of this product. Also, the Applicant performed a Phase 1 study to characterize the PK of the proposed 500 mg dosage strength following administration of Dalbavancin 1500 mg by intravenous infusion in healthy volunteers (DUR001-101).
- g. *Does the Applicant rely on the safety and/or efficacy of a reference product?***  
No. This NDA is a 505 (b) (1) and the Applicant will rely on its own trials for the safety and/or efficacy determination.
- h. *Was a bioequivalence study conducted? If yes, is a Biopharmaceutics Review needed for the submission?***  
No, a bioequivalence study was not conducted and is not needed because the proposed product was used in the Phase 3 trials.

### D) BIOWAIVER

- i. *Is there a waiver request for the submission of in vivo BA/BE data (biowaiver)?***  
No, a biowaiver for BE/BA studies is not needed, as the proposed formulation (500 mg) was studied in the Phase 3 clinical trials and in Phase I study to characterize its pharmacokinetics.
- j. *What is the purpose of the biowaiver request?***  
NA
- k. *What information supports the biowaiver request?***  
NA
- l. *What is the reference drug product?***  
Not applicable, as this NDA is 505(b) (1) and the proposed formulation (500 mg strength) is studied in the two Phase 3 trials being relied on for the safety and efficacy determination and in Phase I study to characterize the pharmacokinetics of the proposed formulation.
- m. *Is the reference product an official Reference Listed Drug Product (RLD)?***  
NA
- n. *What is the formulation of the reference product?***  
NA
- o. *Are there any differences in the formulations of the proposed and the reference drug product?***  
NA
- p. *Do the proposed or reference product contain excipients that can affect the disposition and/or distribution of the drug?***  
NA

*q. What is the difference in pH, administered volume, and osmolarity of the proposed and the reference drug product?*

NA

*r. Are the CFR requirements for granting a biowaiver met? If not, are the provided justification and supportive data appropriate?*

NA

*s. Is the overall information supporting the biowaiver request acceptable?*

NA

*t. Is the biowaiver granted?*

NA

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HOUDA MAHAYNI  
03/04/2014

ANGELICA DORANTES  
03/04/2014

### CLINICAL PHARMACOLOGY REVIEW ADDENDUM

<b>NDA: 021-883</b>	Submission Date(s): 09/26/13
<b>Drug</b>	Dalbavancin
<b>Trade Name</b>	DALVANCE
<b>OCP Reviewer</b>	Yang He, Ph.D.
<b>OCP Team Leader</b>	Kimberly Bergman, Pharm.D.
<b>PM Team Leader</b>	Jeffry Florian, Ph.D.
<b>OCP Division</b>	DCP4
<b>OND division</b>	DAIP
<b>Sponsor</b>	Durata Therapeutics, Inc.
<b>Relevant IND(s)</b>	IND 60613
<b>Submission Type; Code</b>	Original New Drug Application (New Molecular Entity); Resubmission/After Withdrawal
<b>Formulation; Strength(s)</b>	Single-use, clear glass vials containing sterile powder equivalent to 500 mg of anhydrous dalbavancin
<b>Indication</b>	For the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms
<b>Dosage and Administration</b>	1000 mg IV followed one week later by 500 mg IV infused over 30 min

## BACKGROUND

Dalbavancin is a lipoglycopeptide antibacterial drug and is active against susceptible Gram-positive microorganisms, including *Staphylococcus aureus* (including methicillin-resistant strains [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, Group G Streptococci and viridans group streptococci. The original New Drug Application (NDA) for dalbavancin was submitted on 12/21/2004, but withdrawn by the Sponsor on 09/15/2008 (refer to the original clinical pharmacology review dated 12/21/2004, attached in Attachment 1 for reference). Durata Therapeutics, Inc. resubmitted the NDA on 09/26/2013 to market the same drug product for acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms. The clinical pharmacology related materials in the resubmission of dalbavancin NDA were reviewed (refer to clinical pharmacology review dated 03/2014). The purpose of this addendum is as follows:

1. To document the communications with the Sponsor regarding the final decision of the dalbavancin susceptibility breakpoint against *Staphylococcus aureus*.
2. To provide assessment of dalbavancin exposure for patients in the Phase 3 trials, in order to evaluate the potential contribution of exposure to hepatic toxicity. This assessment addressed a concern about hepatotoxicity in 9 patients from the recent Phase 3 trials (DUR001-301 and DUR001-302), as raised by the clinical reviewer during the NDA review process.
3. To provide labeling recommendations on the dalbavancin label proposed by the Sponsor.

## 1 Communication with the Sponsor Regarding the Breakpoint against *S. aureus*

In the current dalbavancin NDA resubmission, the Sponsor relied on a clinical PK/PD model predicted response analysis to determine the dalbavancin breakpoint. The details of this analysis can be found in the clinical pharmacology review dated 03/2014.

A relationship was identified between free AUCavg/MIC as a two-group variable and efficacy endpoint of clinical success at Test of Cure (TOC) in the univariable PK/PD analysis, using exposure and efficacy data from a previously conducted Phase 3 study (VER001-09). Briefly, a threshold of free AUCavg/MIC was determined in order to achieve a statistically significant difference in the clinical response rates at TOC between patients above and patients below the threshold. The AUCavg was defined as dalbavancin AUC over 120 hours divided by 5. Subsequently, this PK/PD relationship and Monte Carlo simulation based on a previously-developed population PK model were used to inform dalbavancin susceptibility interpretive criteria for *S. aureus*. The Sponsor proposed a breakpoint of 0.25 mcg/mL based on the analysis results.

However, our review revealed that the proposed univariable relationships between efficacy endpoints and free AUCavg/MIC were mathematically bounded by the percentage of patients  $<$  or  $\geq$  AUCavg/MIC threshold. For example, using the univariable clinical PK/PD relationship for clinical success at TOC results in a predicted response rate that will never fall below the percentage for patients  $<$  AUCavg/MIC threshold (which is 89.1% for clinical success at TOC in the Sponsor's analysis result) with increasing MIC values. As such, interpreting these predicted response rates based on the PK/PD relationship for clinical success at TOC in the context of a threshold percentage (i.e. 90% cutoff) was deemed not appropriate for dalbavancin breakpoint determination.

More importantly, very limited clinical efficacy data are available for patients with MIC  $\geq$  0.25 mcg/mL (n=3) in all Phase 3 trials combined, although the clinical successful rates in these patients were high. Thus, the Sponsor proposed clinical PK/PD analysis and clinical efficacy data are not supportive of the dalbavancin breakpoint of 0.25 mcg/mL.

In order to assist our assessment in the proposed rationale for breakpoint interpretation, an information request was sent to the Sponsor on 04/28/2014 requesting further justification of using this clinical PK/PD analysis approach, as follows.

**Information Request from FDA:**



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When using the more conservative target values (static: 265 and 2-log kill: 332), a nonclinical target attainment analysis conducted by the reviewer recommended breakpoint of 0.12 - 0.25 mcg/mL. However, the reviewer also concurred with the Sponsor's reanalysis for this nonclinical target attainment analysis, which supported a breakpoint of 0.25 mcg/mL, since the lower target values associated with less frequent dosing regimen were considered reasonable.

The concern still exists regarding the very limited patients (n=3) with MIC of 0.25 mcg/mL in all Phase 3 studies combined, even though the nonclinical target attainment analysis was supportive.

In the teleconference with the Sponsor on 05/15/2014, the Agency described our position and the concern about insufficient clinical data available to support a breakpoint of 0.25 mcg/mL, due to lack of patients with MIC higher than 0.25 mcg/mL. The Agency further recommended a breakpoint of 0.12 mcg/mL for *S. aureus*, based on microbiology surveillance data, nonclinical target attainment analysis, and clinical evidence. The Sponsor understood the concerns regarding the insufficient number of patients with MIC  $\geq$  0.25 mcg/mL in the Phase 3 studies and agreed with the Agency's recommendation of a breakpoint of 0.12 mcg/mL for *S. aureus*.

## **2 ASSESSMENT OF DALBAVANCIN EXPOSURE IN PATIENTS EXPERIENCING HEPATIC TOXICITY**

During NDA review, the clinical reviewer found that a total of 9 patients with normal or < 2x ULN baseline levels of transaminase (ALT or AST) showed transaminase elevations greater than 3x or 5x ULN following dalbavancin treatment in the two recent Phase 3 studies (DUR001-301 and DUR001-302). The frequency of liver transaminase elevation in dalbavancin groups was relatively higher than that in comparator group (vancomycin/ linezolid), which led to a concern of hepatic toxicity with dalbavancin administration. Although an evaluation of dalbavancin exposures in these patients would have been ideal, no PK assessment was included in the two Phase 3 trials.

Alternatively, a population PK model based on PK data from a previous Phase 3 study (VER001-09) was reviewed and considered reasonable for the purpose of describing dalbavancin PK in ABSSSI patients. Thus, by using a PK modeling and simulation approach and patient's demographics from the two recent Phase 3 studies, dalbavancin exposure in these 9 patients was predicted in order to evaluate the potential relationship between exposure and liver transaminase elevations.

The previously derived PopPK parameters were used for simulation by setting inter-individual variability as zero, as presented in Table 2.1. The details of the PopPK model can be found in the clinical pharmacology review dated 03/2014. Table 2.2 shows demographics of the 9 patients with elevated liver transaminases and the doses they received in the Phase 3 trials, which were incorporated in the PopPK simulation.

Table 2.1. Final Population PK Model Parameter Estimates

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
Non Renal CL (L/hr)	$\Theta_1$	0.0199 (40.7)	NA
Renal CL (L/hr)	$\Theta_2$	0.0261 (32.3)	
Vc (L)	$\Theta_3$	3.77 (3.3)	NA
Vp1 (L)	$\Theta_4$	9.28 (5.2)	NA
Vp2 (L)	$\Theta_5$	7.80 (74.0)	NA
Q2 (L/hr)	$\Theta_6$	0.492 (10.4)	NA
Q3 (L/hr)	$\Theta_7$	0.0129 (22.2)	NA
FAC2 – ALB on CL	$\Theta_8$	-1.26 (30.4)	NA
FAC3 – BSA on CL	$\Theta_9$	1.39 (37.7)	NA
FAC5 – SEX on CL	$\Theta_{10}$	1.21 (8.20)	NA
FAC6 – CRCL on CL	$\Theta_{11}$	0.618 (35.1)	NA
FAC8 – ALB on Vc	$\Theta_{12}$	-0.483 (18.7)	NA
FAC9 – BSA on Vc	$\Theta_{13}$	1.10 (10.1)	NA
FAC11 – SEX on Vc	$\Theta_{14}$	1.11 (3.80)	NA
FAC13 – AGE on Vp1	$\Theta_{15}$	0.551 (18.1)	NA
FAC14 – ALB on Vp1	$\Theta_{16}$	-0.772 (21.5)	NA
FAC15 – BSA on Vp1	$\Theta_{17}$	0.869 (18.3)	NA
CCV Residual Error (as %CV)			23.9 (3.8)

Source: revised\_reduced\_S.smr

Abbreviations: AGE = patient age; ALB = albumin; BSA = body surface area; CCV = constant coefficient of variation; CL = clearance; CRCL = creatinine clearance; CV = coefficient of variation; FAC = magnitude of covariate effects (as shown in Equation 12); hr = hour; NA = not applicable; Q2 = first inter-compartmental clearance; Q3 = second inter-compartmental clearance; SE = standard error; Vc = central volume of distribution; Vp1 = first peripheral volume of distribution; Vp2 = second peripheral volume of distribution

\* - SE given as %CV

**Table 2.2.** Demographics of the 9 Patients in the PK simulation

<b>Patient ID</b>	<b>Dose (Day1/Day8, mg)</b>	<b>Age (years)</b>	<b>Sex</b>	<b>Body Surface Area (m2)</b>	<b>Albumin (g/dL)</b>	<b>Creatinine Clearance (mL/min)</b>
121075	1000/500	54	Male	2.017	3.7	107.0
737120	1000/500	48	Male	2.046	3.9	96.7
747505	1000/500	27	Male	1.842	3.9	114.6
763270	1000/na	56	Female	1.708	3.1	103.5
927051	1000/500	42	Male	1.943	4	55.6
927428	1000/500	47	Female	1.815	3.5	83.4
944360	1000/500	82	Female	1.633	2.6	26.9
958055	1000/500	31	Male	2.205	4.3	103.0
958315	1000/500	31	Male	2.179	2.8	48.7

Simulated concentration-time profiles of these subjects were plotted with comparison to the mean PK profile of the patients in the PopPK analysis, as depicted in Figure 2.1. The C<sub>max</sub>, AUC from 0 to 48 hours (AUC<sub>48</sub>), AUC from 0 to 72 hours (AUC<sub>72</sub>), AUC from 0 to 120 hour (AUC<sub>120</sub>), AUC from 0 to 168 hour (AUC<sub>168</sub>), and AUC from 0 to 360 hours (AUC<sub>360</sub>) were also summarized in Table 2.3.

The simulation result indicated that the dalbavancin exposure of these 9 patients were similar to a typical patient who was hypothetically assigned with mean PK parameters, after receiving the same dose. One patient (Patient ID=763270) received only the first 1000 mg dalbavancin on Day 1 but not the second 500 mg dose on Day 8. So, it is reasonable that exposures of this patient before Day 8 were comparable to others but AUC<sub>360</sub> was smaller.

Thus, dalbavancin exposure was not shown to be associated with the post-dose elevation in transaminases (ALT or AST) that was observed in patients receiving dalbavancin. The reason for this post-dose transaminases elevation following dalbavancin administration remains unknown.

Figure 2.1 Simulated dalbavancin concentration-time profiles for the 9 patients with elevated liver transaminases (blue solid circles), compared to the mean PK profile in the patients in the PopPK analysis (red line).

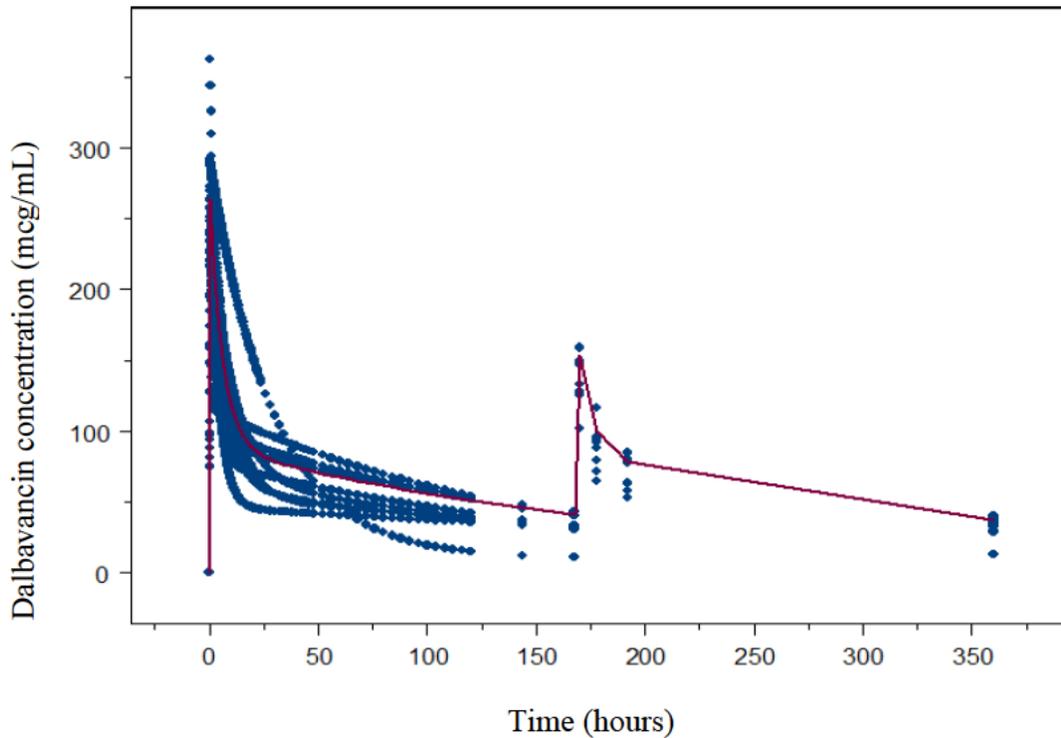


Table 2.3 Simulated dalbavancin exposure from the 9 subjects and a typical patient with population mean of PK parameters

PID	C <sub>MAX</sub> (mcg/mL)	AUC <sub>48</sub> (mcg*hr/mL)	AUC <sub>72</sub> (mcg*hr/mL)	AUC <sub>120</sub> (mcg*hr/mL)	AUC <sub>168</sub> (mcg*hr/mL)	AUC <sub>360</sub> (mcg*hr/mL)
121075	234.34	4612.07	6343.42	9189.60	11391.33	23147.50
737120	291.04	7091.06	8224.05	9278.81	9874.62	19978.65
747505	269.68	4880.86	6774.01	9801.90	12061.94	24068.76
763270 <sup>a</sup>	240.93	4773.38	6018.27	8117.78	9798.22	9798.22
927051	362.86	4071.38	5444.97	7729.22	9521.51	19280.59
927428	292.23	4409.94	5508.52	7477.33	9192.82	19818.69
944360	272.79	3052.35	4026.57	5831.71	7465.04	16874.19
958055	257.76	4665.24	6333.05	9174.14	11477.59	23948.54
958315	220.45	3780.31	4911.89	6865.45	8477.68	17698.78
Typical patient <sup>b</sup>	264.26	4901.52	6520.45	9263.85	11473.26	23709.02

a, this patient received only the first 1000 mg dalbavancin.

b, a hypothetical patient with mean PK parameters.

### 3 DETAILED LABELING RECOMMENDATIONS

The reviewer's recommendations on the sponsor's proposed product labeling are presented below. Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

#### 7. DRUG INTERACTIONS

##### 7.1 Drug-Laboratory Test Interactions

Drug-laboratory test interactions have not been reported.

##### 7.2 Drug-Drug Interactions

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

(b) (4)

### 12. CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Dalbavancin is an antibacterial drug [see (b) (4) Clinical Pharmacology (12.4)].

#### 12.2 Pharmacodynamics

The antibacterial activity of dalbavancin appears to best correlate with the ratio of area under the concentration-time curve to minimal inhibitory concentration (AUC/MIC) for *Staphylococcus aureus* based on animal models of infection. An exposure-response analysis of a single study in patients with complicated skin and skin structure infections supports (b) (4) [see (b) (4) Usage and Administration (2.1) and Clinical Pharmacology (12.3)].

**Cardiac Electrophysiology:** In a randomized, positive- and placebo-controlled, thorough QT/QTc study, 200 healthy subjects received (b) (4) dalbavancin 1000 mg IV, dalbavancin 1500 mg IV, oral moxifloxacin 400 mg, or placebo. Neither dalbavancin

1000 mg, nor dalbavancin 1500 mg (supratherapeutic dose) had any [clinically relevant](#) adverse effect on cardiac repolarization.

### 12.3 Pharmacokinetics

Dalbavancin pharmacokinetic parameters have been characterized in healthy subjects, patients, and <sup>(b) (4)</sup> [specific](#) populations. Pharmacokinetic parameters following administration of a single intravenous 1000 mg dose were as shown in Table 3. <sup>(b) (4)</sup> [The](#) pharmacokinetics of dalbavancin <sup>(b) (4)</sup> [-](#) can be described using a three-compartment model <sup>(b) (4)</sup>

**Table 3. Dalbavancin Pharmacokinetic Parameters in Healthy Subjects**

Parameter	Single 1000 mg Dose
$C_{max}$ (mg/L)	287 (13.9) <sup>1</sup>
AUC <sub>0-24</sub> (mg•h/L)	3185 (12.8) <sup>1</sup>
AUC <sub>0-Day7</sub> (mg•h/L)	11160 (41.1) <sup>2</sup>
AUC <sub>0-∞inf</sub> (mg•h/L)	23443 (40.9) <sup>2</sup>
<a href="#">Terminal</a> t <sub>1/2</sub> (h)	346 (16.5) <sup>2,3</sup>
CL (L/h)	0.0513 (46.8) <sup>2</sup>

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

<sup>1</sup> Data from 50 healthy subjects.

<sup>2</sup> Data from 12 healthy subjects.

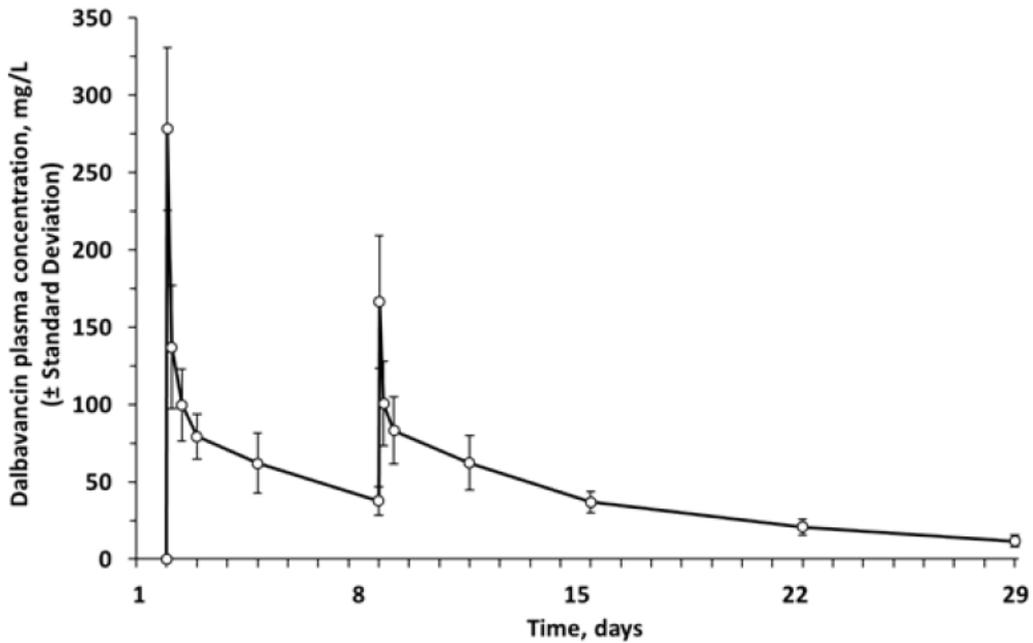
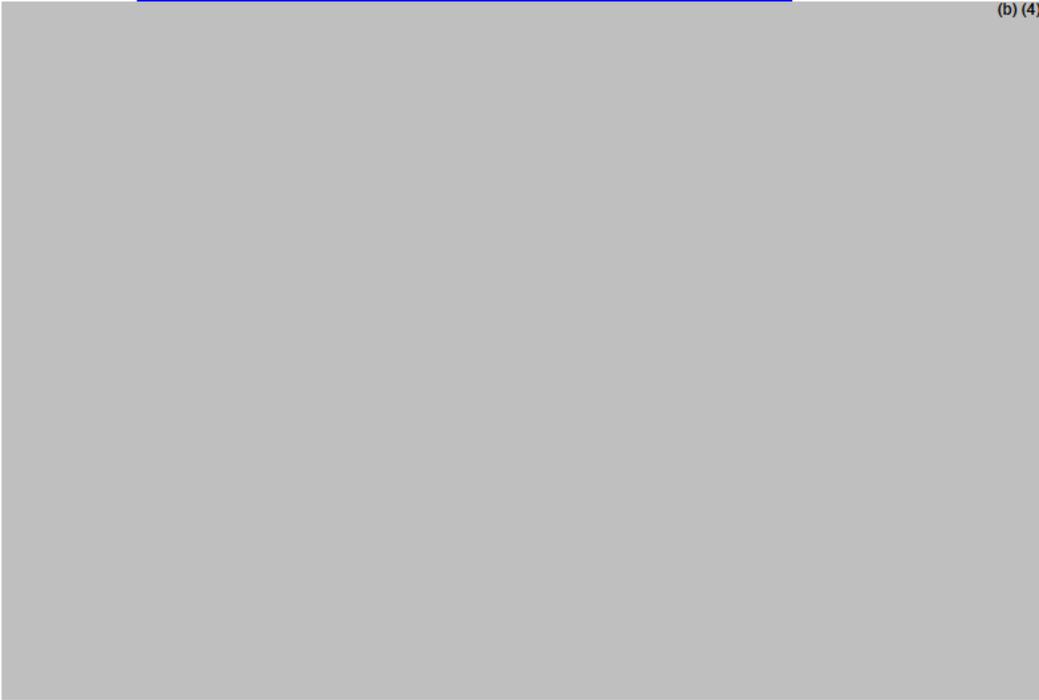
<sup>3</sup> <sup>(b) (4)</sup> Based upon population pharmacokinetic analyses of data from patients, the effective half-life is approximately 8.5 days (204 hours).

In <sup>(b) (4)</sup> healthy subjects, dalbavancin AUC<sub>0-24h</sub> and C<sub>max</sub> both increased <sup>(b) (4)</sup> [proportionally](#) to dose following single [IV](#) dalbavancin doses ranging from 140 mg to <sup>(b) (4)</sup> [1500](#) mg, indicating linear pharmacokinetics.

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

The mean plasma concentration-time profile for dalbavancin at the recommended <sup>(b) (4)</sup> two-dose regimen of 1000 mg followed one week later by 500 mg is shown in Figure 2.

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



**Distribution:** Dalbavancin is reversibly bound to human plasma proteins, primarily to albumin. The plasma protein binding of dalbavancin is approximately 93% and is not altered as a function of drug concentration, renal impairment, or hepatic impairment. The mean concentrations of dalbavancin achieved in skin blister fluid remain above 30 mg/L up to 7 days (approximately 146 hours) post dose. (b) (4) following 1000 mg IV dalbavancin (b) (4). The mean ratio of the AUC<sub>0-144 hrs</sub> in skin blister fluid/AUC<sub>0-144 hrs</sub> in plasma is 0.60 (range 0.44 to 0.64).



**Metabolism:** In vitro studies using human microsomal enzymes and hepatocytes indicate that dalbavancin is not a substrate, inhibitor, or inducer of (b) (4) (CYP450) isoenzymes. (b) (4)

A minor metabolite of dalbavancin (hydroxy-dalbavancin) has been observed in the urine of healthy subjects. Quantifiable concentrations of the hydroxy-dalbavancin metabolite have not been observed in human plasma (lower limit of quantitation = 0.4 µg (b) (4)/mL) [see (b) (4) [Drug Interactions \(7.2\)](#)].

**Excretion:** Following administration of a single 1000 mg dose in healthy subjects, 20% of the dose was excreted in feces through 70 days post dose. (b) (4) An average of (b) (4) 33% of the administered dalbavancin dose was (b) (4) excreted in urine as unchanged dalbavancin and (b) (4) approximately (b) (4) 12% of the administered dose was (b) (4) excreted in urine as the metabolite hydroxy-dalbavancin through 42 days post dose (b) (4)

### (b) (4) **Specific Populations**

(b) (4) **Renal Impairment:** The pharmacokinetics of dalbavancin were evaluated in 28 subjects with varying degrees of renal impairment and in 15 matched control subjects with normal renal function. Following a single dose of 500 mg or 1000 mg dalbavancin, the mean plasma clearance (CL<sub>T</sub>) was reduced 11%, 35%, and 47% in subjects with mild (CL<sub>CR</sub> 50-79 mL/min), moderate (CL<sub>CR</sub> 30-49 mL/min), and severe (CL<sub>CR</sub> (b) (4) less than 30 mL/min) renal impairment, respectively, compared to subjects with normal renal function. (b) (4)



(b) (4) The clinical significance of the decrease in mean plasma  $CL_T$  and the associated increase in  $AUC_{0-\infty}$  noted in these pharmacokinetic studies of dalbavancin in subjects with severe renal impairment have not been established (b) (4)

*-[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].*

No dosage adjustment is necessary for patients with CLCR greater than 30 mL/min or patients receiving hemodialysis. The recommended two-dose regimen for dalbavancin in patients with severe renal impairment who are not receiving regularly scheduled hemodialysis is 750 mg followed by 375 mg. (b) (4)

Dalbavancin pharmacokinetic parameters in subjects with end-stage renal disease receiving regularly scheduled hemodialysis (three times/week) are similar to those observed in subjects with mild to moderate renal impairment, and less than 6% of an administered dose is removed after three hours of hemodialysis. Therefore, no dosage adjustment is recommended for patients receiving regularly scheduled (b) (4) hemodialysis, and dalbavancin may be administered without regard to the timing of (b) (4) hemodialysis in such patients (b) (4)

*-[see Dosage and Administration (2.1) and Overdosage (10)].*

(b) (4) **Hepatic Impairment:** The pharmacokinetics of dalbavancin were evaluated in 17 subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B or C) and compared to those in nine (b) (4) matched healthy subjects with normal hepatic function. The mean  $AUC_{0-336 \text{ hrs}}$  was unchanged in subjects with mild hepatic impairment compared to subjects with normal hepatic function; however, the mean  $AUC_{0-336 \text{ hrs}}$  decreased 28% and 31% in subjects with moderate and severe hepatic impairment respectively, compared to subjects with normal hepatic function. The clinical significance of the decreased  $AUC_{0-336 \text{ hrs}}$  in subjects with moderate and severe hepatic function is unknown.

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

(b) (4)

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

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

**Pediatric Patients:** The pharmacokinetics of dalbavancin in pediatric populations <12 years of age have not been established. (b) (4)



### Drug Interactions

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

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and 362, respectively, well above the 265 free-drug AUC:MIC ratio target identified by Andes and Craig.

- c. Pre-clinical modeling may be more useful at this time relative to modeling based on extrapolations from human data given the challenge of modeling uncommon events, specifically patients with MICs of 0.12 µg/mL and 0.25 µg/mL from the clinical trials.
3. Practical considerations related to standard in vitro MIC testing require some margin of error be acknowledged in the breakpoint for dalbavancin relative to the distribution of MICs identified in surveillance studies which were heavily weighted towards 0.06 µg/mL:
    - a. A breakpoint close to 0.06 µg/mL could inadvertently declare certain strains as non-susceptible which, based on clinical experience, have been found to be effectively treated by the proposed dose of dalbavancin.
    - b.
    - c. The distribution of MICs for the reference strain for *S. aureus* can vary by two tube dilutions.

### Reference

1. Andes D, Craig W. Antimicrobial Agents and Chemotherapy, May 2007, p. 1633–1642

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**ATTACHMENT 1.**

**Office of Clinical Pharmacology Review of NDA 21-883 Original Submission Dated  
12/21/2004**

193 Pages Have Been Withheld As A Duplicate Copy Of The "Clinical Pharmacology and Biopharmaceutics Review" signed 9/20/2005 Which Is Located In This Section Of This NDA Approval Package

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NDA#	21-883 (N-000)
PRODUCT	Dalbavancin (b) (4)
FORMULATION	Sterile lyophilized powder for injection, (b) (4) 500 mg vials
SUBMISSION DATES	12/21/04, 2/17/05, 2/24/05, 5/17/05, 5/18/05, 6/15/05, 8/2/05
SUBMISSION TYPE	Original New Drug Application (NME), Priority Review
SPONSOR	Vicuron Pharmaceuticals, Inc., King of Prussia, PA 19406
OCPB DIVISION	Division of Pharmaceutical Evaluation III
MEDICAL DIVISION	Division of Anti-Infective Drug Products
REVIEWERS	Charles R. Bonapace, Pharm.D. and Vikram Arya, Ph.D.
PM REVIEWER	Bruce Green, Ph.D.
TEAM LEADER	Venkat R. Jarugula, Ph.D.
PM TEAM LEADER	Joga Gobburu, Ph.D.

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## CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

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## 1. EXECUTIVE SUMMARY

Vicuron Pharmaceuticals, Inc. submitted a New Drug Application to market dalbavancin for injection for the treatment of complicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, (b) (4) (b) (4). This NDA was granted a priority review status. The proposed dosage regimen of dalbavancin in adults is 1000 mg IV on day 1 and 500 mg IV on day 8 infused over 30 min.

Dalbavancin is a lipoglycopeptide antibiotic structurally related to teicoplanin, a glycopeptide antibiotic. Dalbavancin consists of a mixture of 5 closely related homologues (A<sub>0</sub>, A<sub>1</sub>, B<sub>0</sub>, B<sub>1</sub>, and B<sub>2</sub>) which share the same core structure. The homologues are all microbiologically active and differ from one another in the length and/or branching of their respective fatty acid side chains on the N-acylaminoglucuronic acid moiety and/or the presence of an additional methyl group on the N-terminus of the peptide. However, two homologues (B<sub>0</sub> and B<sub>1</sub>) compose approximately (b) (4) of the drug product. (b) (4)

Characteristics of dalbavancin include a predominantly Gram-positive spectrum of *in vitro* bactericidal activity. The selection of a weekly dalbavancin dosage regimen was based on PK/PD data from animal models of infection and humans. Dose fractionation experiments using a neutropenic mouse thigh infection model (with *Staphylococcus aureus* and *Streptococcus pyogenes*) demonstrated that the same total dose was more efficacious when administered as larger, less frequent individual doses than when administered as smaller, more frequent individual doses. (b) (4)

In another Phase 2 clinical trial, the sponsor demonstrated that the clinical efficacy of weekly dalbavancin (1000 mg on day 1 and 500 mg on day 8) exceeded the clinical efficacy of a single dose of dalbavancin (1100 mg) for the treatment of uncomplicated and complicated skin and skin structure infections (94% vs. 62%, respectively).

The sponsor performed eight Phase 1 studies to assess single and multiple dose pharmacokinetics, the excretion and metabolism, penetration into skin blisters, and the impact of renal and hepatic impairment. The impact of demographics (age, gender, race, and weight) and concomitant medications on the pharmacokinetics of dalbavancin were assessed from the population pharmacokinetic analysis. Two Phase 2 and three Phase 3 clinical studies were performed to evaluate the safety and efficacy of dalbavancin for the treatment of catheter-related blood stream infections, uncomplicated skin and skin structure infections, and complicated skin and skin structure infections. The most commonly observed adverse events in clinical studies consisted of nausea, diarrhea, headache, constipation, and vomiting.

### 1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III (OCPB/DPE-III) has reviewed NDA 50-797 and it is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

**1.2 PHASE IV COMMITMENTS:**

No Phase IV commitments are recommended.

**1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS****Analytical**

(b) (4)

**Pharmacokinetics in Healthy Subjects**

Following the administration of dalbavancin in single- and multiple-dose studies, the mean  $C_{max}$  and AUC increased nearly proportional to dose. The mean  $CL_T$  and  $V_{SS}$  remained relatively constant across all doses and after multiple-dose administration. Following the administration of 1000 mg infused over 30 min, the mean  $C_{max}$  and  $AUC_{0-t}$  were approximately 340  $\mu\text{g/mL}$  and 24,453  $\mu\text{g}\cdot\text{hr/mL}$ , respectively.

**Pharmacokinetics in Patients with Infections**

The mean central and peripheral volumes of distribution were 28% and 67% higher, respectively in patients with infections compared to healthy subjects. The mean plasma clearance was 43% higher and the inter-compartmental clearance 15% higher in patients with infections compared to healthy subjects.

**Distribution**

After intravenous administration of 1000 mg, 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 concentrations.

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 skin blister concentrations on days 1 (12 hrs), 3 (50 hrs), 5 (98 hrs), and 7 (146 hrs) were 72.7, 59.5, 39.5, and 33.4  $\mu\text{g/mL}$ , respectively. The mean percent penetration of dalbavancin in skin blister fluid was 60% based on the  $AUC_{0-7\text{days}}(\text{blister fluid})/AUC_{0-7\text{days}}(\text{plasma})$ .

**Metabolism**

Based on *in vitro* assays using human microsomal enzymes, dalbavancin is not a substrate or inhibitor of cytochrome P450 isoenzymes. A study in rats receiving 10 mg/kg/day dalbavancin for 7 days showed no induction of any cytochrome P450 isoenzyme.

A minor metabolite of dalbavancin (OH-dalbavancin) has been observed in the urine of healthy subjects and is below the assay LLOQ in plasma. OH-dalbavancin appears to have less antimicrobial activity than any of the five components of dalbavancin ( $A_0$ ,  $A_1$ ,  $B_0$ ,  $B_1$ , and  $B_2$ ).

**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.

**Pharmacokinetics in Special Populations****Renal impairment**

The impact of mild, moderate, and severe renal impairment as well as end-stage renal disease (ESRD) on the pharmacokinetics of dalbavancin were assessed in three clinical studies. The mean  $CL_T$  decreased 11% and 35% and the mean  $AUC_{0-\infty}$  increased 10% and 53% in subjects with mild and moderate renal impairment, respectively compared to subjects with normal renal function. Among subjects with severe renal impairment, the mean  $CL_T$  decreased approximately 50% and the mean  $AUC_{0-\infty}$  increased approximately 100% compared to subjects with normal renal function.

The mean  $CL_T$  was reduced 39% in subjects with ESRD compared to subjects with normal renal function when dalbavancin was administered prior to hemodialysis, whereas the mean  $CL_T$  was reduced 19% when dalbavancin was administered following hemodialysis. The mean  $AUC_{0-\infty}$  increased 62% and 28% for subjects with ESRD receiving dalbavancin pre-dialysis and post-dialysis, respectively compared to subjects with normal renal function. After correction for body weight, the  $CL_T$  (L/hr/kg) was reduced approximately 20% for both groups of ESRD subjects compared to subjects with normal renal function. Dalbavancin was not appreciably removed after 3 hrs of hemodialysis. No dosage adjustment is recommended for patients with mild or moderate renal impairment and ESRD. Based on simulated individual concentration-time profiles from subjects with normal renal function (n=15) and mild (n=6), moderate (n=6), and severe (n=10) renal impairment, the proposed dosage regimen for patients with severe renal impairment is 750 mg on day 1 and 375 mg on day 8.

**Hepatic impairment**

The pharmacokinetics of dalbavancin were 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  $C_{max}$  and  $AUC_{0-\infty}$  were similar in subjects with mild hepatic impairment compared to control subjects. However, the mean  $C_{max}$  (day 1) and  $AUC_{0-\infty}$  decreased 18% and 30%, respectively in subjects with moderate hepatic impairment and 29% and 36%, respectively in subjects with severe hepatic impairment compared to subjects with normal hepatic function. The mean  $CL_T$  increased 39% and 58% in subjects with moderate and severe hepatic impairment, respectively. The mean elimination half-life of dalbavancin remained unchanged.

**Elderly/Gender/Race**

The impact of covariates such as age, gender, and race on the pharmacokinetics of dalbavancin were evaluated with the population pharmacokinetic 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 yrs of age, among male and female patients, and race.

**Drug-Drug Interactions**

Based on the findings from *in vitro* metabolism studies that dalbavancin is neither an inhibitor nor a substrate of cytochrome P450 isoenzymes, the sponsor did not perform any clinical drug-drug interaction studies. However, the sponsor assessed the administration of concomitant medications and medication groups as covariates with the population pharmacokinetic analysis. No clinically relevant differences in the pharmacokinetics of dalbavancin were observed when dalbavancin was administered alone and when co-administered with known CYP P450 inhibitors, substrates, and inducers as well as additional drugs.

**Exposure-Response****Neutropenic mouse thigh infection model**

The unbound  $AUC_{0-24 \text{ hrs}}/\text{MIC}$  was the PK/PD parameter best associated with in vivo efficacy based on the neutropenic thigh infection model. For the dalbavancin regimens utilizing q24h dosing, the unbound  $AUC_{0-24 \text{ hrs}}/\text{MIC}$  associated with a static effect against *S. pneumoniae* and *S. aureus* were  $17.6 \pm 6.9$  and  $265 \pm 143$ , respectively.

For the regimens that utilized less frequent dosing (q72h), the unbound  $AUC_{0-24 \text{ hrs}}/\text{MIC}$  values associated with a static effect against *S. pneumoniae* and *S. aureus* were  $7.2 \pm 4.5$  and  $160 \pm 67$ , respectively.

**Monte Carlo simulation**

(b) (4)

**Population Pharmacokinetic Analysis**

(b) (4)

(b) (4)



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RD/FT Initialed by Venkat R. Jarugula, Ph.D., \_\_\_\_\_  
Team Leader

cc:

Division File: NDA 21-883

HFD-520 (CSO/Davi)

HFD-520 (MO/Nambiar, Pohlman, Imoisili)

HFD-880 (Division File, Lazor, Selen, Jarugula, Bonapace, Arya)

HFD-860 (Gobburu)

CDR (Clin. Pharm./Biopharm.)

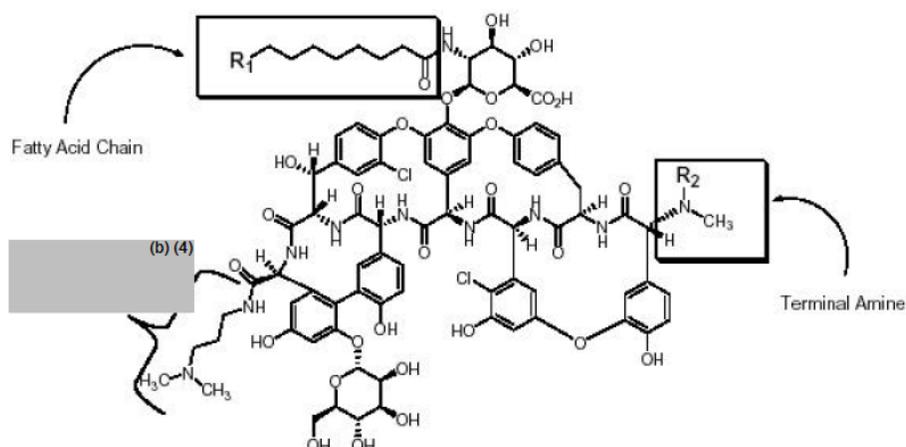
## 2. QUESTION-BASED REVIEW

### 2.1 General attributes of the drug

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Dalbavancin is a semi-synthetic antibiotic manufactured by chemical modification of the natural glycopeptide antibiotic A-40926, which is produced by aerobic fermentation by *Nonomuria* spp. Dalbavancin active pharmaceutical ingredient (API) is a mixture of 5 closely related homologues ( $A_0$ ,  $A_1$ ,  $B_0$ ,  $B_1$ , and  $B_2$ ), which all share the same core structure (Figure 1). These homologues differ from one another in the length and/or branching of their respective fatty acid side chains on the N-acylaminoglucuronic acid moiety at position 56 (designated as  $R_1$ ) and/or the presence of an additional methyl group (designated as  $R_2$ ) on the N-terminus of the peptide (Table 1). The major API component (b) (4) is dalbavancin  $B_0$ . The empirical formula of dalbavancin ( $B_0$  component) is  $C_{88}H_{100}Cl_2N_{10}O_{28}$  and the molecular weight is 1816.7.

**Figure 1. Structure of dalbavancin active pharmaceutical ingredient (API)**



**Table 1. Components of dalbavancin API**

Factor	Composition	$R_1$	$R_2$
$A_0$	(b) (4)	$CH(CH_3)_2$	H
$A_1$	(b) (4)	$CH_2CH_2CH_3$	H
$B_0$	(b) (4)	$CH_2CH(CH_3)_2$	H
$B_1$	(b) (4)	$CH_2CH_2CH_2CH_3$	H
$B_2$	(b) (4)	$CH_2CH(CH_3)_2$	$CH_3$

The five API components of dalbavancin have similar *in vitro* microbiological activity against common Gram-positive organisms (e.g., *S. aureus*, *S. epidermidis*, *S. pyogenes*, *S. pneumoniae*, and *E. faecalis*). MAG, the principal degradation product of dalbavancin, has reduced microbiological activity (b) (4) against Gram-positive organisms compared to the API components.

The solubility of dalbavancin in buffer is shown in Table 2. Since the solubility of dalbavancin is approximately 20  $\mu\text{g/mL}$  in buffer at physiologic pH (b) (4)

(b) (4) the sponsor was requested to provide data supporting the solubility of dalbavancin in plasma. It appears that the solubility of dalbavancin is higher in plasma than in pH matched buffer and may be related to the degree of protein binding (93%). According to the sponsor's response, (b) (4)

**Table 2. Impact of pH on the solubility of dalbavancin in buffer**

pH	Buffer	Solubility (mg/mL)
(b) (4)		

**2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?**

Like other glycopeptides, dalbavancin interferes with cell wall formation by binding to the terminal D-alanyl-D-alanine (D-ala-D-ala) of the stem peptide in nascent peptidoglycan, inhibiting cross-linking. This appears to be the only relevant action that dalbavancin exerts on bacteria. Because this target structure is not found in mammalian cells, dalbavancin is not expected to have secondary pharmacology effects.

The proposed therapeutic indication of dalbavancin is complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* including methicillin-resistant and multidrug-resistant (MDR) strains, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus* (b) (4)

Dalbavancin is active against many Gram-positive bacterial pathogens, including methicillin-resistant (MR) and multidrug-resistant (defined as resistant to at least 3 different classes of antimicrobial agents) staphylococci, coagulase-negative staphylococci with reduced susceptibility to teicoplanin, and streptococci resistant to penicillin. Dalbavancin activity has been demonstrated against vancomycin-intermediate *S. aureus* (VISA), *in vitro* and in animal models, and against at least 1 vancomycin-resistant *S. aureus* (VRSA) strain *in vitro* at concentrations that are sustained in patients. Dalbavancin is also active against vancomycin-susceptible enterococci as well as vancomycin-resistant enterococci with the exception of phenotypically VanA strains.

**2.1.3 What are the proposed dosage(s) and route(s) of administration?**

The proposed dosage regimen of dalbavancin for adults is 1000 mg on day 1 and 500 mg on day 8 for the treatment of complicated skin and skin structure infections administered as an intravenous infusion over 30 min. Dalbavancin is supplied as a sterile lyophilized powder in (b) (4) 500 mg single-use vials to be reconstituted for intravenous administration.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor performed eight Phase 1 studies to assess the single dose and multiple dose pharmacokinetics, effect of renal impairment [mild, moderate, severe, and ESRD], effect of hepatic impairment [mild, moderate, and severe], tissue penetration into healthy skin assessed with skin biopsy and cantharidin-induced skin blisters, and metabolic profiling in plasma, urine, and feces.

The sponsor performed two Phase 2 clinical studies evaluating the safety and efficacy of dalbavancin for the treatment of catheter-related blood stream infections (Study VER001-4) and uncomplicated and complicated skin and skin structure infections (Study VER001-5) as well as three Phase 3 clinical studies evaluating the safety and efficacy of dalbavancin for the treatment of uncomplicated skin and skin structure infections (Study VER001-8), complicated skin and skin structure infections (Study VER001-9), and uncomplicated and complicated skin and skin structure infections (VER001-16) as shown in Table 3. Studies VER001-4, VER001-5, and VER001-16 were randomized, open-label, multicenter trials whereas studies VER001-8 and VER001-9 were randomized, double-blind, multicenter trials.

**Table 3. Phase 2 and Phase 3 clinical trials used to support dosing claims**

Study #	Indication(s)	Dalbavancin regimen	Comparator regimen	Endpoint
VER001-4 (Phase 2)	CRBS infections with suspected or confirmed Gram-positive infections	Dalbavancin 1000 mg on day 1, then optional 500 mg on day 8 (n=33) or dalbavancin 650 mg on day 1, then 65 mg/day for days 2-14 (n=7)	Vancomycin 1000 mg q12h for 7-14 days (n=34)	TOC visit 21±3 days after the end of therapy
VER001-5 (Phase 2)	uSSSI and cSSSI	Dalbavancin 1100 mg on day 1 (n=20) or dalbavancin 1000 mg on day 1, then 500 mg on day 8 (n=21)	Investigator designated comparator (n=21)	TOC visit 14±2 days after the end of therapy
VER001-8 (Phase 3)	uSSSI	Dalbavancin 1000 mg on day 1, then optional 500 mg on day 8 (n=367)	Cefazolin 500 mg IV q8h for 7-14 days (n=186)	TOC visit 14 days after the end of therapy
VER001-9 (Phase 3)	cSSSI	Dalbavancin 1000 mg on day 1, then 500 mg on day 8 (n=571)	Linezolid 600 mg IV q12h for 14 days (n=283)	TOC visit 14±2 days after the end of therapy
VER001-16 (Phase 3)	uSSSI and cSSSI	Dalbavancin 1000 mg on day 1, then optional 500 mg on day 8 (n=107)	Vancomycin 1000 mg IV q12h for 14 days (n=49)	TOC visit 14±2 days after the end of therapy

CRBS = catheter-related blood stream; uSSSI - uncomplicated skin and skin structure infections; cSSSI - complicated skin and skin structure infections.

In study VER001-4, patients with pathogens other than *S. aureus* and with catheters removed could be treated with a single dose of dalbavancin (1000 mg on day 1). In study VER001-16, investigators had the option of treating patients with uSSSI with a single dose of dalbavancin or 7 days of comparator.

### 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in the Phase 3 studies (VER001-8, VER001-9, and VER001-16) was the clinical response at the test of cure (TOC) visit in the clinically evaluable population. Secondary efficacy endpoints consisted of the clinical response, microbiological response, and overall response for the ITT, micro ITT, clinically evaluable, and microbiologically evaluable populations.

**Phase 2 Studies VER001-4, VER001-5**

Clinical outcome was assessed as success (clinical cure or improvement) or failure (persistence, death, or indeterminate [no post-baseline local or systemic signs and symptoms available to assess]).

Microbiological outcome was assessed as success (eradication or presumed eradication) or failure (persistence, presumed persistence, or indeterminate).

**Phase 3 Studies VER001-8, VER001-9, VER001-16**

Clinical outcome was assessed as success (sufficient resolution of the local and systemic signs and symptoms), failure (persistence of one or more local or systemic signs and symptoms or death), or indeterminate (no post-baseline local or systemic signs and symptoms data were available).

Microbiological outcome was assessed as success (eradication or presumed eradication) or failure (persistence, presumed persistence, or indeterminate).

**2.2.3 Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

(b) (4)



In addition, a hydroxy metabolite of dalbavancin (OH-dalbavancin) with antimicrobial activity has been quantitated in urine. The concentrations of B<sub>0</sub> and B<sub>1</sub> have been quantitated in clinical studies from plasma, urine, and skin blister fluid; the concentration of OH-dalbavancin has only been quantitated in urine. The concentration of dalbavancin in fecal samples was determined using a microbiological assay and is based on all active moieties.

(b) (4)


**2.2.4 Exposure-response****2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.**

The exposure-response relationship of dalbavancin has been evaluated using *in vitro* time-kill studies, *in vivo* animal models of infection, and human microbiological and clinical efficacy data. Time-kill studies were used to assess the impact of bacterial killing for dalbavancin over time against clinical isolates. Clinical isolates evaluated consisted of two methicillin-susceptible *Staphylococcus aureus* (MSSA)

isolates, three methicillin-resistant *S. aureus* (MRSA) isolates, one vancomycin-intermediate *S. aureus* (VISA) isolate, one *Streptococcus pyogenes* isolate, and one vancomycin-susceptible *Enterococcus faecalis* isolate. Dalbavancin was tested in time-kill studies at concentrations of 0.25, 1, 4, and 16 µg/mL. Dalbavancin exhibited concentration-dependent bactericidal activity ( $\geq 3$ -log<sub>10</sub> reduction of the initial inoculum) against the methicillin-susceptible and methicillin-resistant *S. aureus* isolates, the *S. pyogenes* isolate, and a 2.5 log<sub>10</sub> reduction in viable bacteria against the vancomycin-susceptible *Enterococcus faecalis* isolate.

#### **Animal Infection Model:**

The impact of the dosing regimen on the in vivo efficacy of dalbavancin was assessed using the murine neutropenic thigh infection model in Study VER001-M1-013. The investigators evaluated the association between common PK/PD parameters (e.g., peak serum concentration to MIC ratio [ $C_{\max}$ /MIC], area under the concentration-time curve to MIC ratio [AUC/MIC], and the duration of interval that serum concentrations exceed the MIC [T >MIC]) with in vivo efficacy of dalbavancin and determined whether the magnitude of the principal PK/PD parameter associated with specified endpoints were similar among common Gram-positive bacteria including penicillin-resistant *S. pneumoniae* and methicillin-resistant *S. aureus* (MRSA). In addition, the effect of infection site on the activity of dalbavancin was evaluated against both *S. pneumoniae* and *S. aureus* in the thigh and pneumonia animal infection models.

#### **Pharmacokinetics:**

Swiss ICR mice were rendered neutropenic with cyclophosphamide (150 mg/kg 4 days prior to study, 100 mg/kg 1 day prior to study, and 100 mg/kg every 48 hrs until the end of the study (day 6). The pharmacokinetics of dalbavancin were assessed following the administration of 2.5, 5, 10, 20, 40, and 80 mg/kg via intraperitoneal injection. The AUC was estimated at 24, 36, 48, 72, 96, and 144 hrs and extrapolated to infinity. The 24 hr AUC was calculated as the 6-day AUC (144 hrs) divided by 6. The half-life of dalbavancin varied from 7.6 hrs to 13.1 hrs. The degree of protein binding was estimated at 99.6% in mouse serum and 96% in human serum.

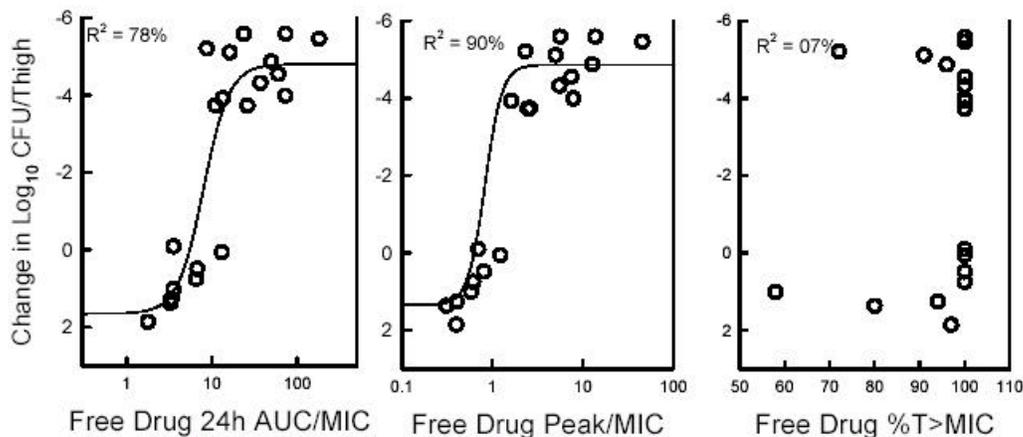
#### **Dose Fractionation Studies:**

Two hrs before starting therapy, mice were infected with the specified organisms. For the thigh infection model, each thigh was infected with approximately 10<sup>6</sup> CFUs (actual inoculum at the start of the experiment ranged from 10<sup>7.15</sup> to 10<sup>7.59</sup> CFUs/thigh). The lung infection model was used with only a single isolate of either *S. pneumoniae* or *S. aureus*. Mice were infected by intranasal inoculation of approximately 10<sup>8.5</sup> CFUs (actual inoculum at the start of the experiment ranged from 10<sup>7.4</sup> to 10<sup>7.6</sup> CFUs/lung).

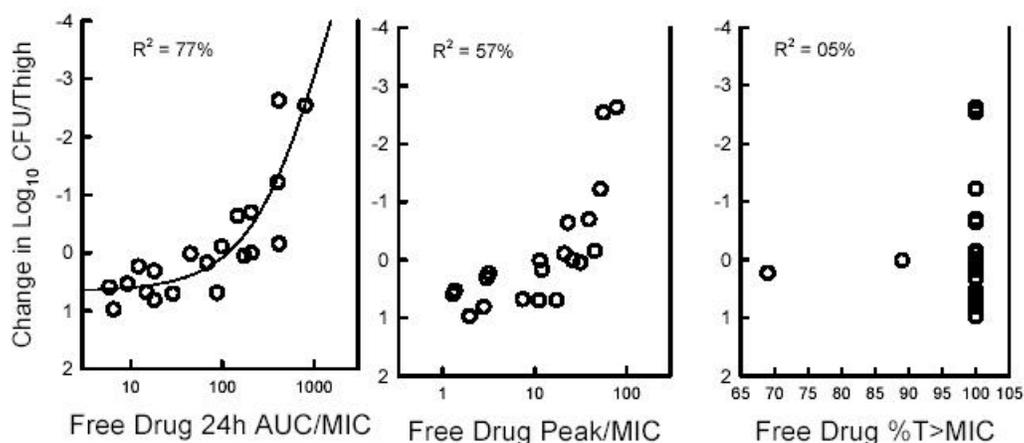
Dose fractionation studies were performed by varying the dose and the dosing interval. The selected dosing intervals were q12h, q24h, q36h, and q72h for 6 days. Five different doses (two-fold increments) were used ranging from 30 to 480 mg/kg/6 days for *S. aureus* and 0.6125 to 10 mg/kg/6 days for *S. pneumoniae*. The dose-response curves were analyzed using an Emax model to determine the dose required to produce a static effect, 1 log<sub>10</sub> reduction, and 2 log<sub>10</sub> reduction in organism burden.

The relationships between unbound dalbavancin AUC<sub>0-24 hrs</sub>/MIC,  $C_{\max}$ /MIC, and T>MIC and the log<sub>10</sub> change in the number of viable organisms for *S. pneumoniae* and *S. aureus* in the thighs of neutropenic mice after 144 hrs of therapy are shown in Figures 2 and 3. Each point represents the mean of four thighs. The static dose and the dose associated with a 1-log<sub>10</sub> and 2-log<sub>10</sub> kill for each of the drug organism combinations and the various dosing regimens are shown in Table 4.

**Figure 2. Relationship between dalbavancin PK/PD parameters and efficacy for *S. pneumoniae* in the neutropenic mouse thigh infection model**



**Figure 3. Relationship between dalbavancin PK/PD parameters and efficacy for *S. aureus* in the neutropenic mouse thigh infection model**



The unbound  $AUC_{0-24 \text{ hrs}}/MIC$  and  $C_{max}/MIC$  were the PK/PD parameters that were best associated with in vivo efficacy of the neutropenic thigh infection model regression of the data although the  $AUC_{0-24 \text{ hrs}}/MIC$  ratio resulted in the strongest correlation with *S. aureus*. This study was not capable of evaluating  $T > MIC$  since all but two regimens resulted in 100%  $T > MIC$ . In general, increasing the dosing interval resulted in a slight shift of the dose response curves to the left indicating more efficacy with the regimens for which large doses were administered infrequently. Increasing the dosage interval from 12 to 36 hrs against *S. pneumoniae* did not result in an appreciable change in the doses associated with the three microbiologic endpoints. However, efficacy with the 72 hrs dosing interval required less drug. A similar relationship was observed in study against *S. aureus*. The only dosing regimens that produced a 1- $\log_{10}$  and 2- $\log_{10}$  kill against *S. aureus* were the 36 and 72 hr dosing intervals.

**Table 4. Mean (95% CI) dalbavancin dosages (mg/kg/6 days) required to achieve a static effect (SD), 1-log<sub>10</sub>, and 2-log<sub>10</sub> net kill for four different dosing intervals in a *S. pneumoniae* and *S. aureus* infection models**

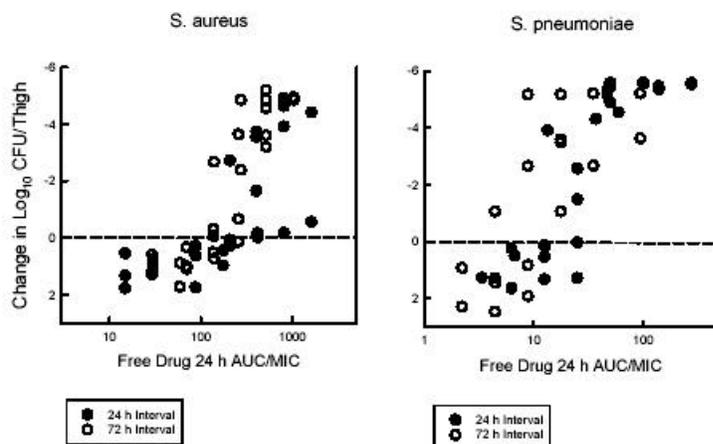
Organism	q12h			q24h			q36h			q72h		
	SD	1-log <sub>10</sub> kill	2-log <sub>10</sub> kill	SD	1-log <sub>10</sub> kill	2-log <sub>10</sub> kill	SD	1-log <sub>10</sub> kill	2-log <sub>10</sub> kill	SD	1-log <sub>10</sub> kill	2-log <sub>10</sub> kill
SP10813	2.3 (1.9 to 2.7)	2.8 (2.3 to 3.3)	3.5 (2.8 to 4.2)	1.34 (1.14 to 1.57)	1.54 (1.34 to 1.74)	1.75 (1.47 to 2.03)	1.26 (1.16 to 1.36)	1.53 (1.41 to 1.65)	1.81 (1.67 to 1.95)	0.71 (0.64 to 0.88)	0.77 (0.59 to 0.95)	0.82 (0.62 to 1.02)
SA29213	80 (8 to 152)	---	---	26 (39 to 91)	267 (400 to 934)	---	15 (14 to 44)	36 (34 to 106)	122 (117 to 361)	10 (18 to 38)	31 (55 to 117)	128 (230 to 486)

#### PK/PD Parameter Magnitude:

To determine if the  $AUC_{0-24 \text{ hrs}}/MIC$  required for a static effect was similar for multiple pathogens, the in vivo activity of 24- and 72-hr dosing regimens of dalbavancin against 5 strains of *S. pneumoniae* and 6 strains of *S. aureus* after 6 days of therapy were assessed. The dalbavancin MICs ranged from 0.004 to 0.03  $\mu\text{g/mL}$  for *S. pneumoniae* and 0.06-0.12  $\mu\text{g/mL}$  for *S. aureus*.

In general, the shape of the dose-response curves (q24h and q72h) was similar for all strains (Figure 4). However, the dose response curves for *S. pneumoniae* were shifted slightly to the left. This curve shift suggests that less drug was necessary to produce a similar effect against *S. pneumoniae* compared to *S. aureus*. The extent of bacterial killing was relatively similar for most strains.

**Figure 4. Dose-response curves of dalbavancin against 6 strains of *S. aureus* (left) and 5 strains of *S. pneumoniae* (right)**



For the dalbavancin regimens utilizing every 24 hr dosing, the unbound  $AUC_{0-24 \text{ hrs}}/MIC$  associated with a static effect against *S. pneumoniae* and *S. aureus* were  $17.6 \pm 6.9$  and  $265 \pm 143$ , respectively. The  $AUC_{0-24 \text{ hrs}}/MIC$  values associated with a 1 and 2 log<sub>10</sub> kill were not appreciably higher. Therapy against *S. pneumoniae*, based upon the  $AUC_{0-24 \text{ hrs}}/MIC$ , required 12- to 23-fold less drug, as suggested by the dose response curves.

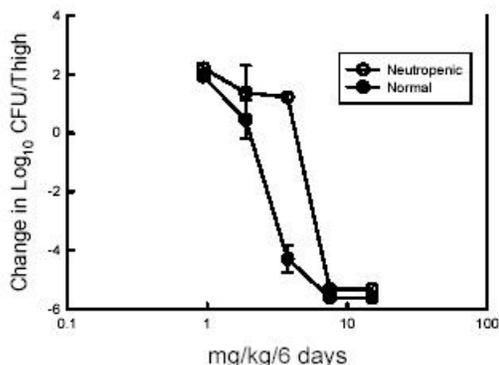
For the regimens that utilized less frequent dosing (every 72 hrs), the unbound  $AUC_{0-24 \text{ hrs}}/MIC$  values associated with a static effect against *S. pneumoniae* and *S. aureus* were  $7.2 \pm 4.5$  and  $160 \pm 67$ , respectively. The PK/PD magnitudes necessary to achieve the three PK/PD endpoints (static dose, 1 log<sub>10</sub>, and 2 log<sub>10</sub> net kill) were lower for 72 hr dosing interval compared to the 24 hr dosing interval.

When dalbavancin was dosed every 24 hrs, the  $AUC_{0-24\text{ hrs}}/MIC$  values associated with the various endpoints were 1.3- to 2.4-fold higher than when dalbavancin was dosed every 72 hrs.

**Impact of Neutrophils:**

To determine the effect of neutrophils on the activity of dalbavancin, the dose-response curves with 24 hr dosing intervals in both normal and neutropenic mice infected with *S. pneumoniae* were compared (Figure 5). The absence of neutrophils resulted in a 1.7- to 2.1-fold increase in the doses necessary for efficacy. However, these differences were not statistically significant.

**Figure 5. Impact of neutrophils on the in vivo activity of dalbavancin against *S. pneumoniae* in a thigh infection model**



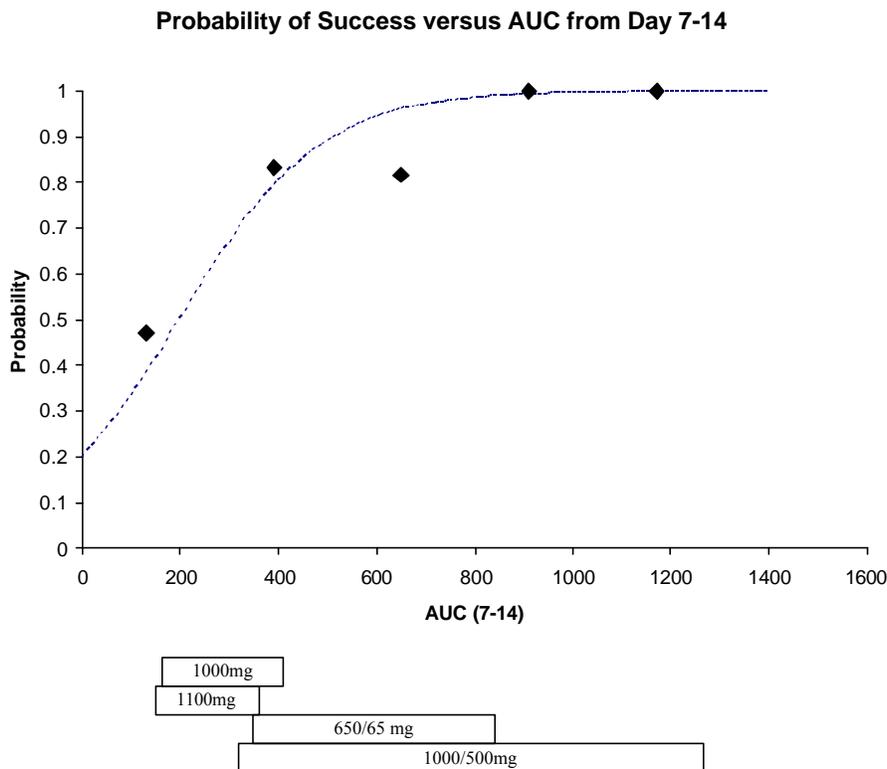
**Impact of Infection Site:**

To determine the impact of infection site on the activity of dalbavancin, the dose-response curves with the 24 hr dosing interval in both the thigh and lung infection models were compared. The dose-response curves in the two models utilizing *S. pneumoniae* were nearly identical. In contrast, the *S. aureus* dose response curve in the lung model was shifted to the left compared to the thigh infection model, suggesting less drug is necessary for efficacy at this site of infection. However, the confidence intervals in the staphylococcal study were large and these differences were not significant.

**Monte Carlo Analysis:**



**Figure 9. Probability of clinical success vs. AUC<sub>8-14 days</sub> following administration of 1000 mg, 1100 mg, 650 mg loading dose and 65 mg/day for 14 days, and 1000 mg on day 1 and 500 mg on day 8**



Although the number of patients in the Phase 2 clinical trial VER001-5 was small, dalbavancin 1000 mg on day 1 followed by 500 mg on day 8 was associated with a higher clinical response rate (94%, 16/17) compared to dalbavancin 1100 mg as a single dose (62%, 8/13). The data supported the further evaluation of dalbavancin as a once-weekly regimen in uSSSI (VER001-8) and cSSSI (VER001-9). Since the sponsor never assessed the clinical efficacy of a single 1500 mg dose of dalbavancin, it is unknown if the difference in efficacy among the regimens is due to administration of a second dose or a large total dose (1000 mg or 1100 mg vs. 1500 mg).

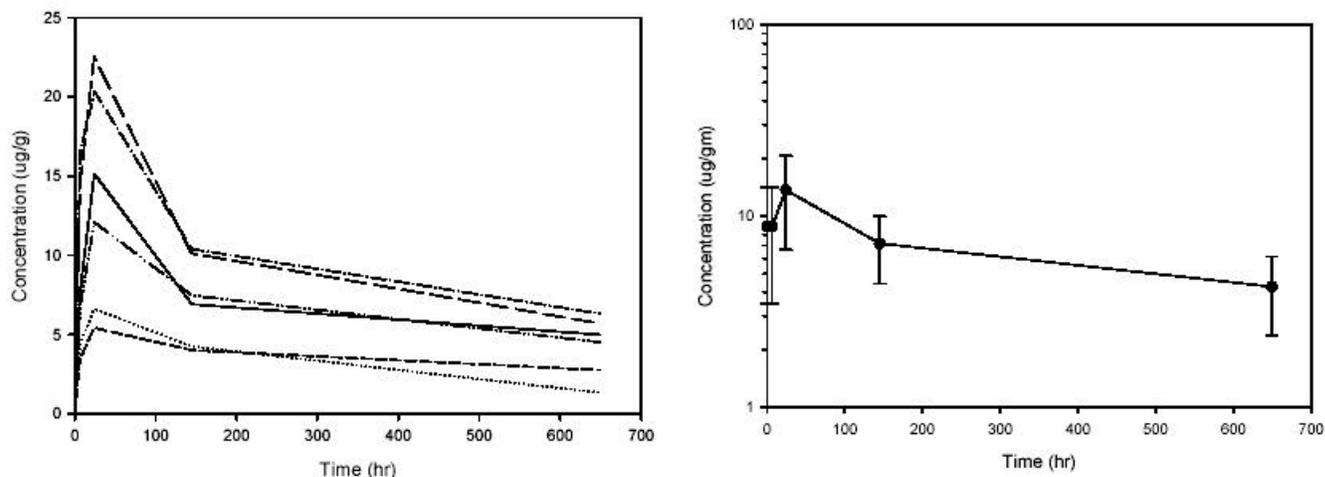
NOTE: *Streptococcus pneumoniae* was evaluated in the neutropenic thigh infection model even though it is not considered a pathogen for skin and skin structure infections. The magnitude of the PK/PD parameter associated with efficacy for *Streptococcus pneumoniae* cannot be extrapolated to an organism relevant to skin and skin structure infections such as *Streptococcus pyogenes*.

#### **Tissue Penetration:**

The sponsor assessed the penetration of dalbavancin into skin using a punch biopsy technique and cantharidin-induced skin blisters. Following the administration 1000 mg dalbavancin IV infused over 30 min in six subjects, the total concentrations of dalbavancin in skin based on skin punch biopsies at pre-dose and on days 1, 2, 7, and 28 are shown in Figure 10. The concentration of dalbavancin in skin peaked on day 2 (mean 13.69 µg/mL) and the mean concentration was 7.19 µg/mL (range 4.01 to 10.39 µg/mL) on day 7. (b) (4)

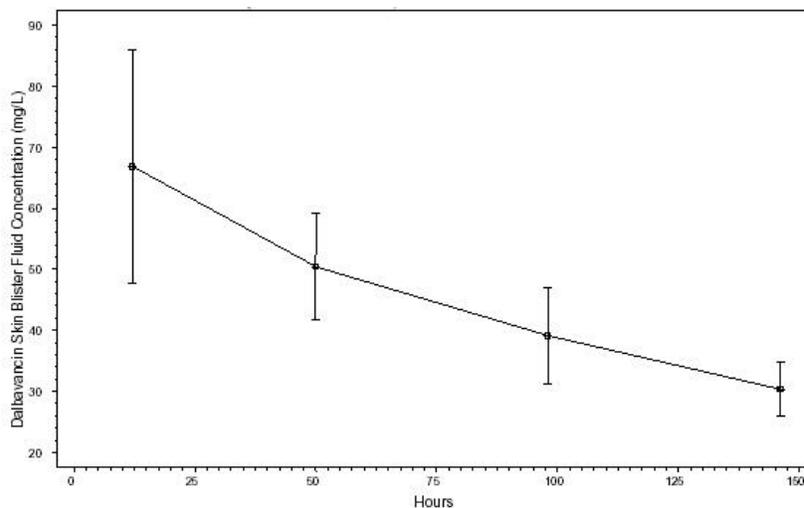
However, the reviewer determined the mean penetration of dalbavancin into skin to be 20% (range 12% to 31%) when the AUC<sub>0-648</sub> was used from skin and plasma. (b) (4)

**Figure 10. Individual (left) and mean (right) dalbavancin skin biopsy concentration-time profiles following administration of a single dose of dalbavancin 1000 mg**



In another study, the penetration of dalbavancin was assessed following administration of 1000 mg dalbavancin IV infused over 30 min with cantharidin-induced blisters at predose and on days 1, 3, 5, and 7. The mean concentration-time profile of dalbavancin in skin blister fluid is shown in Figure 11. The mean penetration of dalbavancin into skin blister fluid was 60% (range 44% to 64%) based on the  $AUC_{\text{blister fluid}}/AUC_{\text{plasma}}$  ratio ( $AUC_{0-144 \text{ hrs}}$  for blister fluid and plasma).

**Figure 11. Mean dalbavancin skin blister fluid concentration-time profiles following administration of a single dose of dalbavancin 1000 mg**



The mean blister fluid concentration remained above 30  $\mu\text{g/mL}$  through 146 hrs (range 19.7 to 34.0  $\mu\text{g/mL}$ ). (b) (4)

, the unbound concentration of dalbavancin at the site of infection (assuming a protein binding of 93%) exceeded 1  $\mu\text{g/mL}$  for at least six days in most subjects following the administration of a single 1000 mg dose of dalbavancin and may exceed 1  $\mu\text{g/mL}$  throughout 14 days of therapy following the administration of 1000 mg of dalbavancin on day 1 and 500 mg on day 8 for some subjects. However, the penetration of dalbavancin into skin may be reduced in patients with skin and skin structure infections due to inflammation, edema, and increased hydrostatic pressure.

**2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.**

In nonclinical studies, target organ toxicities included the kidney, liver and infusion reactions. Based on animal toxicology data and the safety profile of the class, renal, hepatic, and infusion site adverse events (AEs) were closely evaluated in the clinical studies. The only approved glycopeptide on the US market is vancomycin. Although vancomycin is generally well-tolerated, clinically important vancomycin AEs consist of "Red-man" syndrome, seen with rapid infusion; infusion site reactions, characterized by pain and phlebitis; ototoxicity, which manifest as either vestibular or auditory impairment; renal toxicity, which is rarely seen; and myelosuppression.

In Phase 2 and Phase 3 clinical trials, 419 patients received a single dose of dalbavancin 1000 mg and 707 patients received dalbavancin 1000 mg on day 1 followed by 500 mg on day 8. The three most commonly reported AEs in the dalbavancin and comparator treatment groups were nausea, diarrhea, and headache. Please refer to the medical officer's review for complete details on the adverse events of dalbavancin.

**Ototoxicity:**

A total of 105 subjects dosed with dalbavancin in Phase 1 studies have undergone audiologic testing. All audiology data have been reviewed by a single central reviewer. Review of the totality of the data did not suggest any evidence of ototoxicity.

**Hepatic Toxicity:**

The incidence of hepatobiliary disorder AEs was similar between dalbavancin and comparator treated patients. Of the patients who received dalbavancin, 10 (0.9%) had at least 1 hepatobiliary disorder AE, compared with 4 (0.7%) patients who received a comparator. Of these, only 3 (0.3%) in the dalbavancin treatment arm versus 1 (0.2%) in the comparator arm were considered treatment-related. Examination of specific abnormalities in ALT and AST as well as transitions in hepatobiliary parameters during Phase 2 and Phase 3 studies did not suggest a signal of hepatic toxicity due to administration of dalbavancin.

**Renal Toxicity:**

The incidence of renal disorder AEs was similar between patients treated with dalbavancin and patients treated with a comparator. Of the patients who received dalbavancin, 2.6% had at least one renal disorder AE compared with 3.1% of patients who received a comparator drug. Systematic review of renal parameters including BUN and serum creatinine did not suggest nephrotoxicity in patients treated with dalbavancin.

**Infusion-related Toxicity:**

A larger percentage of patients who received a comparator reported infusion-associated AEs than those who received dalbavancin. Thirty-one (2.8%) patients who received dalbavancin and 27 (4.7%) patients who received a comparator had at least one infusion-associated AE. A greater proportion of patients with a longer exposure to study drug had infusion-associated AEs. The most frequently reported infusion-associated AE was infusion site reaction, reported by 0.8% of dalbavancin-treated patients and 1.4% of comparator-treated patients. Red Man syndrome was seen with two vancomycin-treated patients and none of dalbavancin-treated patients.

### 2.2.4.3 Does this drug prolong the QT or QTc interval?

An *in vitro* hERG assay using human embryonic kidney cells (HEK293) was performed to assess the impact of dalbavancin on cardiac repolarization. The concentration of dalbavancin used in the study was 16.9 µg/mL (following the administration of 1000 mg of dalbavancin, the total and unbound C<sub>max</sub> values are approximately 300 µg/mL and 20 µg/mL, respectively). The hERG current was not inhibited at 16.9 µg/mL dalbavancin (0.2% block) compared to 83.9% block for 60 nM terfenadine.

NOTE:

(b) (4)

Based on the preclinical animal data, dalbavancin did not have an effect on blood pressure, heart rate, or QT interval in conscious dogs at doses 3 to 4 times the human dose on a mg/kg basis.

The sponsor has not performed a Phase 1 thorough QT study to assess the impact of dalbavancin on cardiac repolarization. The sponsor assessed ECG data that was collected in several Phase 1 studies (VER001-2, VER001-10, VER001-11, VER001-12, and VER001-13) and Phase 2/3 studies (VER001-4, VER001-5, and VER001-8). Only patients with paired ECG data obtained at baseline and C<sub>max</sub> were evaluated by a centralized expert reviewer in a blinded fashion. Three consecutive ECG complexes were measured, whenever feasible. The following data were summarized: change from baseline in QTcB interval; the number (%) of patients with increased QTcB interval (≤30 msec, >30 to 60 msec, and >60 msec); the number (%) of male patients with post-baseline QTcB interval of <431 msec, 431 to 450 msec, >450 msec, or >500 msec; and the number (%) of female patients with post-baseline QTcB interval of <451 msec, 451 to 470 msec, >470 msec, or >500 msec. All subjects from Phase 1 studies received the proposed dose of dalbavancin or lower except three subjects that received a single dose of 1120 mg. All patients from the Phase 2/3 studies received the proposed dose of dalbavancin or lower except 18 patients in Study VER001-5 that received a single dose of 1100 mg.

#### Phase 1 studies:

For the 113 subjects who received dalbavancin and had paired ECG data (ECGs at baseline and C<sub>max</sub>), the mean change in QTcB from baseline was 2.2 msec (95% CI = -1.8 to 6.2 msec), and ranged from -62 to 59 msec. For the 13 subjects who received placebo and had paired ECG data, the mean change in QTcB interval from baseline was 0.8 msec (95% CI = -16.1 to 17.7 msec) and ranged from -38 msec to 63 msec. Seven (6.2%) subjects who received dalbavancin had an increase in QTcB >30 to 60 msec, compared with 1 (7.7%) subject who received placebo. No subject who received dalbavancin had an increase in QTcB >60 msec compared with one subject who received placebo. No subject (male or female) had a QTcB interval >500 msec. The mean effect on QTcF of subjects who received dalbavancin was 3.2 msec, with a 90% confidence interval ranging from -0.2 to 6.6 msec. Although the mean change in QTcF following treatment was close to 0 msec for placebo, there was a wide confidence interval due to the limited size of the placebo group (n=13).

#### Phase 2/3 studies:

Data from patients receiving dalbavancin in the Phase 3 studies were compared to a group of drugs with no known QT effects. For the 382 dalbavancin-treated patients who had paired ECG data (ECGs at baseline and C<sub>max</sub>), the mean change in QTcB interval from baseline was 0.4 msec (95% CI = -1.7 to 2.4 msec), and ranged from -88 to 95 msec. For the 199 comparator-treated patients who had paired ECG data, the mean change in QTcB interval from baseline was -2.2 msec (95% CI = -5.3 to 0.8 msec), and ranged from -98 msec to 62 msec. There was no meaningful difference between dalbavancin-treated patients and comparator-treated patients for frequency of QTcB outliers observed during drug exposure: 6.3% of dalbavancin-treated patients had an increase in QTcB >30 to 60 msec, compared with 5.5% of

comparator-treated patients, and 0.5% of patients in both treatment groups (dalbavancin and comparator) had an increase in QTcB >60 msec. Two (0.9%) male dalbavancin-treated patients and 1 (0.6%) female dalbavancin-treated patient had a treatment-emergent QTcB interval >500 msec. In comparison, 2 (1.8%) male comparator-treated patients and 1 (1.1%) female comparator-treated patient had a treatment-emergent QTcB interval >500 msec. Regardless of which QT correction method was used (Bazett or Fridericia), the changes in QTc results were minimal. The effect of dalbavancin on QTcF values was close to 0 msec, and was similar to comparator-treated patients (0.4 msec and -0.3 msec, respectively).

The ECG results from the Phase 1 and Phase 2/3 clinical studies were based on a single ECG reading at baseline and after the completion of the infusion. Although the second ECG reading did not always occur at the end of the infusion, it was obtained near the  $C_{max}$ . It is unknown if obtaining ECG recordings at a later timepoint to allow penetration into cardiac tissues would have resulted in different results. However limited, the available data help support the finding that dalbavancin does not appear to exhibit a significant impact on cardiac repolarization following the end of the infusion.

#### **2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

Based on the neutropenic murine thigh infection model, the primary PK/PD parameters that appears to be associated with efficacy of dalbavancin are the  $AUC_{0-24 \text{ hrs}}/MIC$  and  $C_{max}/MIC$ . The  $AUC_{0-24 \text{ hrs}}/MIC$  was best associated with efficacy against *S. aureus*, whereas the  $C_{max}/MIC$  was best associated with efficacy against *S. pneumoniae*. Unlike time-dependent drugs, dose-fractionated studies in the neutropenic thigh infection model demonstrated that increasing the dosing interval of dalbavancin resulted in a shift of the dose response curve to the left (lower total dose associated with the same effect). Thus, it appears that the efficacy of dalbavancin may be higher with regimens for which large doses were administered infrequently. Administration of dalbavancin 1000 mg on day 1 followed by 500 mg on day 8 is consistent with the known PK/PD properties of the drug.

In study VER001-5, dalbavancin 1000 mg on day 1 followed by 500 mg on day 8 was associated with a higher clinical response rate (94%, 16/17) than dalbavancin 1100 mg as a single dose (62%, 8/13). Although the number of patients was small, the data supported the further study of dalbavancin as a once-weekly regimen in uSSSI (VER001-8) and cSSSI (VER001-9). Since the sponsor never assessed the clinical efficacy of a single 1500 mg dose of dalbavancin, it is unknown if the difference in efficacy among the regimens is due to administration of a second dose or a large total dose (1000 mg or 1100 mg vs. 1500 mg). Furthermore, the  $AUC/MIC$  associated with efficacy was lower in the neutropenic thigh infection model compared to the value associated with clinical efficacy.

#### **2.2.5 What are the PK characteristics of the drug and its major metabolite?**

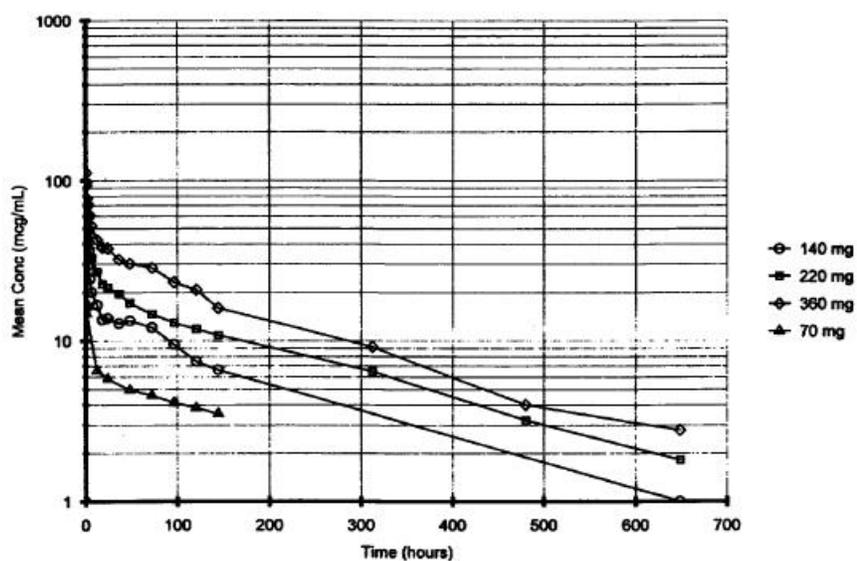
##### **2.2.5.1 What are the single dose and multiple dose PK parameters?**

The pharmacokinetics of dalbavancin were assessed in healthy subjects following the administration of intravenous dalbavancin 70 mg, 140 mg, 220 mg, and 360 mg (Study VER001-1). The plasma concentration-time profiles of dalbavancin are shown in Figure 12. The mean pharmacokinetic parameter estimates based on total dalbavancin concentrations for single-dose and multiple-dose administration are shown in Table 5. The plasma concentrations of the primary metabolite, OH-dalbavancin were below the lower limit of quantitation. The mean  $C_{max}$  increased modestly greater than dose-proportional when normalized by the 70 mg dose and dose proportional when normalized by the 140 mg dose. The mean AUC increased nearly proportional to dose with doses ranging from 70 to 360 mg, whereas the mean  $CL_T$  and  $V_{SS}$  remained relatively constant with increasing dose. The mean  $CL_T$  ranged from 0.0381 to 0.0427

L/hr and was less than the predicted creatinine clearance in subjects with normal renal function (7.5 L/hr). The mean  $t_{1/2}$  ranged from 158 hrs (140 mg) to 186 hrs (70 mg) and did not demonstrate a trend with increasing dose.

The mean plasma concentration-time profiles of dalbavancin on day 1 and day 7 following administration of 70 mg once daily for 7 days are shown in Figure 13. Accumulation of dalbavancin was observed after 7 days of once-daily dosing as the mean  $C_{max}$  increased 134% (20.75  $\mu\text{g}/\text{mL}$  on day 1, 48.54  $\mu\text{g}/\text{mL}$  on day 7) and the mean AUC increased 300% (223  $\mu\text{g}\cdot\text{hr}/\text{mL}$  on day 1, 891  $\mu\text{g}\cdot\text{hr}/\text{mL}$  on day 7). The elimination half-life of dalbavancin on day 7 was similar to values observed following single dose administration; however, the estimated elimination half-life on day 1 may not accurately reflect the actual elimination half-life due to the limited sample times. The predicted accumulation factor assuming once daily administration and an elimination half-life of 194 hrs is 12.2 and supports that the plasma concentrations measured on day 7 were not at steady-state.

**Figure 12. Mean plasma dalbavancin concentration-time profiles following administration of a single dose of dalbavancin 70, 140, 220, and 360 mg**

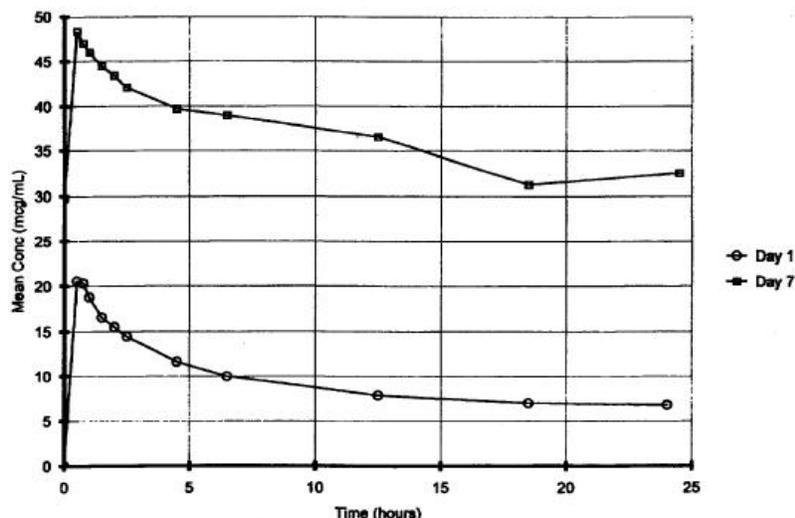


**Table 5. Mean (CV%) dalbavancin pharmacokinetic parameters following administration of 70, 140, 220, and 360 mg single doses and 70 mg daily for 7 days**

Parameter	Single Dose				Multiple Dose (70 mg)	
	70 mg (n=3)	140 mg (n=3)	220 mg (n=3)	360 mg (n=2)	Day 1 (n=6)	Day 7 (n=6)
$C_{max}$ ( $\mu\text{g/mL}$ )	17.31 (11%)	44.84 (6%)	70.39 (17%)	111.86 (8%)	20.75 (11%)	48.54 (9%)
$T_{max}$ (hrs)	0.50 (0%)	0.67 (22%)	0.50 (0%)	0.50 (0%)	0.54 (19%)	0.54 (19%)
$AUC^1$ ( $\mu\text{g}\cdot\text{hr/mL}$ )	1679 (18%)	2548 (17%)	5811 (9%)	8735 (5%)	223 (10%)	891 (9%)
$CL_T$ (L/hr)	0.0427 (20%)	0.0403 (18%)	0.0381 (9%)	0.0413 (5%)	---	0.079 (16%)
$V_{SS}$ (L)	11.02 (25%)	7.35 (15%)	8.80 (21%)	9.47 (13%)	---	---
$t_{1/2}$ (hrs)	186 (15%)	158 (19%)	183 (11%)	168 (8%)	61 (34%)	194 (11%)

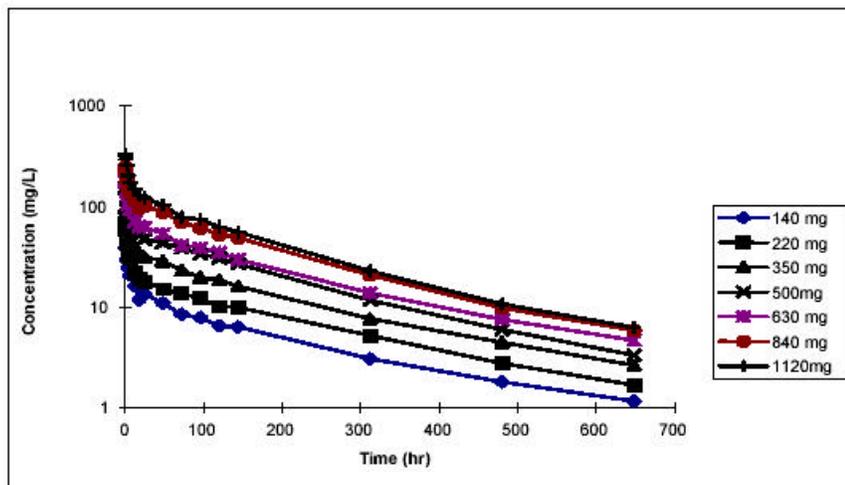
1- $AUC_{0-\infty}$  following single dose administration;  $AUC_{0-24\text{ hrs}}$  and  $AUC_{0-t}$  following multiple-dose administration on day 1 and day 7, respectively.

**Figure 13. Mean plasma dalbavancin concentration-time profiles on day 1 (?) and day 7 (i) following administration of 70 mg once daily for 7 days**



The pharmacokinetics of dalbavancin were assessed in a second study (Study VER001-2) to evaluate the maximum tolerated dose. The starting dose of dalbavancin was 140 mg followed by 220 mg, 350 mg, 500 mg, 630 mg, 840 mg, and 1120 mg. Dose escalation was to proceed up to 1120 mg or the MTD, whichever was encountered first. The mean plasma concentration-time profiles of dalbavancin following a single dose of 140 mg to 1120 mg are shown in Figure 14. The mean dalbavancin plasma concentrations increased with dose, with measurable concentrations in all dose groups observed through the 648 hr time-point (28 days) following dosing.

**Figure 14. Mean plasma dalbavancin concentration-time profiles following administration of a single dose of dalbavancin 140 mg to 1120 mg**



The mean (CV%) plasma pharmacokinetic parameters of dalbavancin following single dose administration are shown in Table 6. The mean  $C_{max}$  and AUC increased proportional to dose between 140 mg and 1120 mg. The mean  $CL_T$  and  $V_{SS}$  remained relatively constant across all doses, although the mean  $V_{SS}$  was somewhat lower with the 500 mg, 840 mg, and 1120 mg doses. The mean  $t_{1/2}$  ranged from 149 hrs (1120 mg) to 189 hrs (140 mg) and did not demonstrate a trend with increasing dose.

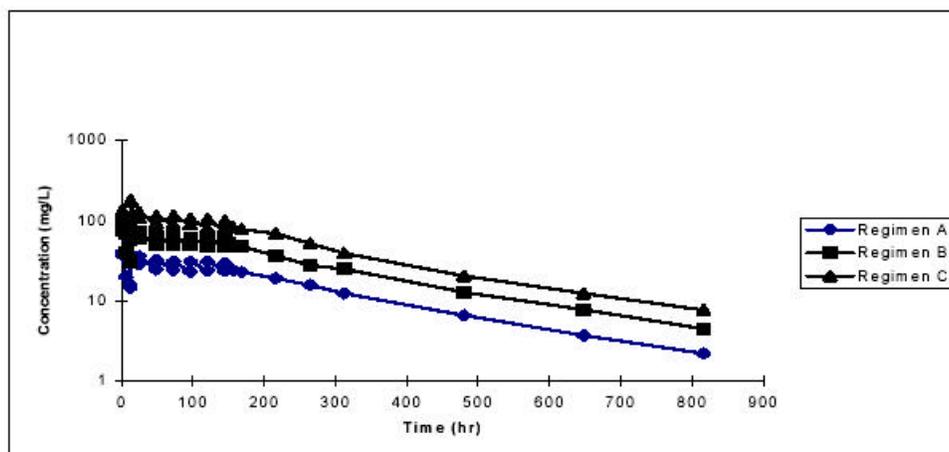
In the multiple-dose phase of the study, dosing consisted of a loading dose (two equal doses given 12 hrs apart on day 1) followed by a maintenance dose. The starting regimen was a loading dose of 300 mg (given as 150 mg q12h on day 1) followed by a maintenance dose of 30 mg once daily for six days. Dose escalation was to proceed as follows: 300/30 mg, 400/40 mg, 600/60 mg, 800/80 mg, 1000/100 mg, or until the MTD was achieved. The mean plasma concentration-time profiles of dalbavancin 300/30 mg, 600/60 mg, and 1000/100 mg infused over 30 min are shown in Figure 15. The mean plasma concentration-time profiles of dalbavancin 400/40 mg and 800/80 mg are shown in Figure 16. The mean plasma concentrations declined in a log-linear manner from about day 8 or 9 through the last sampling time at 4 weeks following the final dose (840 hrs).

The mean plasma pharmacokinetic parameters for each group in the multiple-dose cohorts are shown in Table 7. The mean  $C_{max}$  and  $C_{min}$  values increased nearly proportional to dose over the range from 300 mg to 1000 mg. The mean  $CL_T$  was independent of dose. Although the clearance values following multiple-dose administration were greater than observed following single dose administration, it is likely that subjects were not at steady-state by day 7. The mean elimination  $t_{1/2}$  ranged from 184 hrs (400/40mg) to 198 hrs (600/60mg) and showed no trend with increasing dose.

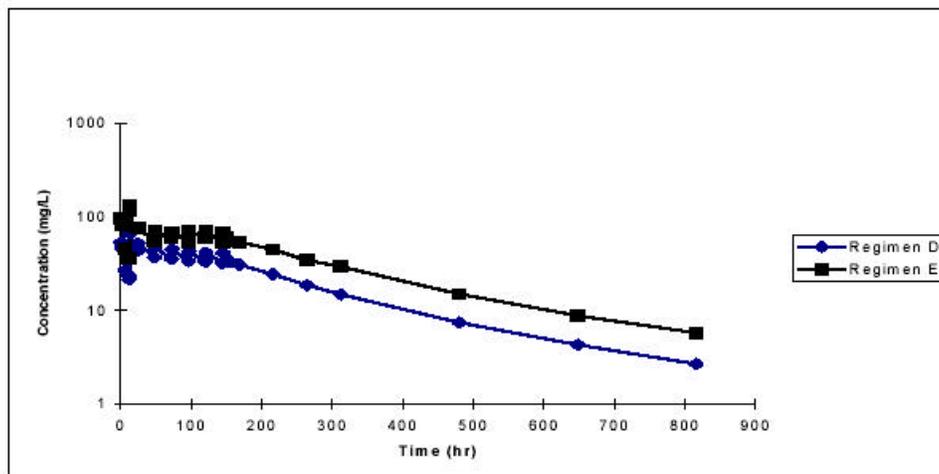
**Table 6. Mean (CV%) dalbavancin pharmacokinetic parameters following single dose administration of dalbavancin infused over 30 min**

Parameter	140 mg (n=3)	220 mg (n=3)	350 mg (n=3)	500 mg (n=3)	630 mg (n=3)	840 mg (n=3)	1120 mg (n=3)
C <sub>max</sub> (µg/mL)	39.7 (4%)	65.3 (23%)	96.1 (7%)	153 (24%)	190 (31%)	243 (5%)	325 (13%)
T <sub>max</sub> (hrs)	0.667 (43%)	0.5 (0%)	0.5 (0%)	0.5 (0%)	0.833 (35%)	0.5 (0%)	0.5 (0%)
AUC (µg*hr/mL)	3251 (3%)	4955 (11%)	8094 (15%)	12451 (16%)	14758 (27%)	22225 (5%)	25790 (9%)
CL <sub>T</sub> (L/hr)	0.0431 (3%)	0.0448 (12%)	0.0439 (15%)	0.0408 (15%)	0.0446 (24%)	0.0379 (5%)	0.0437 (10%)
V <sub>SS</sub> (L)	10.9 (2%)	11.3 (12%)	10.7 (22%)	8.58 (14%)	10.5 (31%)	7.75 (7%)	8.49 (12%)
t <sub>1/2</sub> (hrs)	189 (2%)	188 (9%)	181 (9%)	159 (3%)	172 (9%)	152 (4%)	149 (2%)
CL <sub>R</sub> (L/hr)	0.0146 (21%)	0.0175 (40%)	0.0148 (20%)	0.0115 (26%)	0.0159 (25%)	0.0130 (15%)	0.0151 (40%)
Urinary excretion on day 1 (%)	4.47 (11%)	4.91 (35%)	4.45 (10%)	4.11 (11%)	5.03 (34%)	4.56 (9%)	5.27 (41%)

**Figure 15. Mean plasma dalbavancin concentration-time profiles following administration of 300/30 mg (Regimen A), 600/60 mg (Regimen B), and 1000/100 mg (Regimen C)**



**Figure 16. Mean plasma dalbavancin concentration-time profiles following administration of 400/40 mg (Regimen D) and 800/80 mg (Regimen E)**



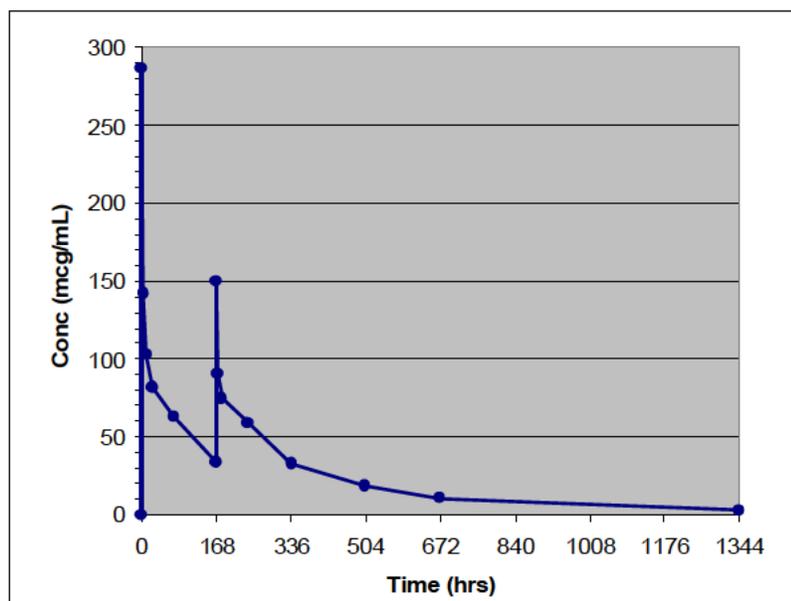
**Table 7. Mean (CV%) dalbavancin pharmacokinetic parameters following multiple dose administration (30 min infusion)**

Parameter	Day	300/30 mg (n=3)	400/40 mg (n=3)	600/60 mg (n=3)	800/80 mg (n=3/2)	1000/100 mg (n=3)
$C_{max}$ ( $\mu\text{g/mL}$ )	1	57.3 (14%)	77.6 (15%)	115.0 (7%)	131.0 (24%)	180.0 (14%)
$C_{min}$ ( $\mu\text{g/mL}$ )	1	14.4 (28%)	21.6 (3%)	30.2 (11%)	36.5 (20%)	57.2 (14%)
$C_{max}$ ( $\mu\text{g/mL}$ )	7	29.6 (18%)	42.3 (18%)	63.7 (5%)	67.7 (3%)	98.9 (19%)
$C_{min}$ ( $\mu\text{g/mL}$ )	7	22.7 (15%)	30.9 (10%)	47.1 (5%)	54.0 (1%)	77.7 (16%)
AUC ( $\mu\text{g}\cdot\text{hr/mL}$ )	7	597 (13%)	825 (10%)	1221 (6%)	1371 (3%)	1997 (16%)
$CL_T$ (L/hr)	7	0.0508 (13%)	0.0489 (11%)	0.0493 (7%)	0.0584 (3%)	0.0509 (14%)
$t_{1/2}$ (hrs)	7	191 (7%)	184 (9%)	198 (9%)	198 (7%)	189 (6%)
$CL_R$ (L/hr)	7	0.0127 (16%)	0.0228 (48%)	0.0150 (20%)	0.0148 (0%)	0.0189 (26%)
Urinary excretion on day 7 (%)*	7	25.0 (14%)	45.5 (35%)	30.6 (23%)	25.4 (5%)	37.1 (18%)

\*based on 24 hr urinary excretion on day 7 divided by the maintenance dose

The pharmacokinetics of dalbavancin following administration of the proposed dosage regimen (1000 mg on day 1 and 500 mg on day 8) have only been assessed in Study VER001-12 (hepatic impairment). The mean plasma concentration-time profile of dalbavancin in healthy subjects following administration of 1000 mg on day 1 and 500 mg on day 8 is shown in Figure 17. Please refer to Section 2.3.2.6 Hepatic Impairment for pharmacokinetic parameter estimates.

**Figure 17. Mean plasma dalbavancin concentration-time profile following administration of 1000 mg on day 1 and 500 mg on day 8 infused over 30 min**



#### **2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compared to that in patients?**

The sponsor performed a population pharmacokinetic analysis to describe the pharmacokinetics of dalbavancin in patients with catheter-related blood stream infections (VER001-4) and skin and skin structure infections (VER001-5 and VER001-9). Plasma concentration-time data from healthy subjects in studies VER001-10 and VER001-19 (1000 mg dalbavancin infused over 30 min) were fit to a 2-compartment model and compared to pharmacokinetic parameters obtained from the sponsor's base model. The mean central and peripheral volumes of distribution were 28% and 67% higher, respectively in patients with infections compared to healthy subjects. The mean plasma clearance was 43% higher and the inter-compartmental clearance 15% higher in patients with infections compared to healthy subjects. Please consult the pharmacometric review for more information on the pharmacokinetics of dalbavancin in patients (see Appendix 4.3. Pharmacometric review).

#### **2.2.5.3 What are the characteristics of drug absorption?**

Dalbavancin is intended to be administered as an intravenous infusion over 30 min.

#### **2.2.5.4 What are the characteristics of drug distribution?**

The plasma protein binding of dalbavancin was assessed using equilibrium dialysis over the concentration range of 1 to 250  $\mu\text{M}$  (1.8 to 454.2  $\mu\text{g/mL}$ ). The mean protein binding is estimated to be 92.6% (range 90.3% to 94.0%) and is independent of the dalbavancin concentration. The sponsor has not addressed previous concerns that dalbavancin is "sticky" and may potentially bind to the dialysis membrane, falsely increasing the estimated protein binding. Thus, the actual protein binding of dalbavancin may be less than the estimated 93%. The protein binding of dalbavancin was not altered in subjects with severe renal or hepatic impairment.

The apparent steady-state volume of distribution ( $V_{SS}$ ) of dalbavancin in healthy subjects ranged from approximately 8 to 11 L and is not dependent upon the administered dose.

**2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

A mass balance study was not performed for dalbavancin due to the prolonged retention of dalbavancin in tissues and vital organs. See Section 2.2.5.7 for characteristics of drug excretion.

**2.2.5.6 What are the characteristics of drug metabolism?**

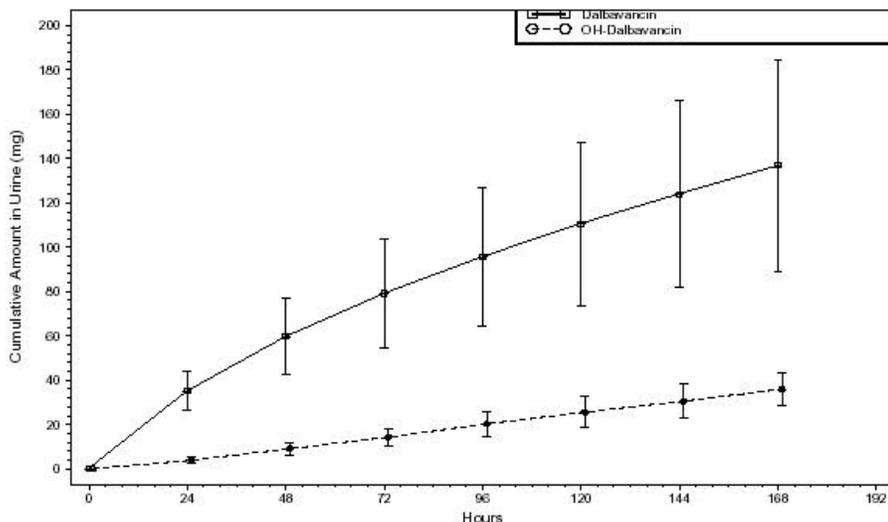
Several *in vitro studies* were performed to assess the induction and inhibition potential as well as the metabolism of dalbavancin. A study in rats receiving 10 mg/kg/day of dalbavancin for 7 days showed no induction of any cytochrome P450 isoenzyme. Dalbavancin was not an inhibitor of cytochrome P450 isoenzymes using human liver microsomes at concentrations up to 20  $\mu\text{M}$  (36.3  $\mu\text{g/mL}$ ).

The primary metabolite of dalbavancin *in vivo* is OH-dalbavancin. Concentrations of OH-dalbavancin are below the assay LLOQ in plasma but are quantifiable in urine. Using *in vitro* methods, dalbavancin was not metabolized following incubation with human hepatocytes; however, 96% of the positive control remained at the end of the experiment. In further studies, dalbavancin was shown to be metabolically stable following incubation with rat, dog, and human liver microsomes or hepatocytes. Dalbavancin was not metabolized following incubation with human kidney microsomes, although 86% of the positive control remained at the end of this experiment. OH-dalbavancin was not been detected in the incubation mixture from any *in vitro* studies.

**2.2.5.7 What are the characteristics of drug excretion?**

The mean cumulative amount of dalbavancin and OH-dalbavancin excreted in urine is shown in Figure 18. Following the administration of a single 1000 mg dose of dalbavancin, approximately 35.0 mg of dalbavancin and 3.8 mg of OH-dalbavancin are excreted in urine within 24 hrs. At the end of 168 hrs (7 days), approximately 136.8 mg of dalbavancin and 35.9 mg of OH-dalbavancin are excreted in urine. The cumulative amount of dalbavancin and OH-dalbavancin excreted in urine collected over 1632 hrs (68 days) was 214.5 mg and 84.2 mg, respectively. Thus, approximately 21% and 8% of an administered dose was excreted in urine as unchanged dalbavancin and OH-dalbavancin, respectively.

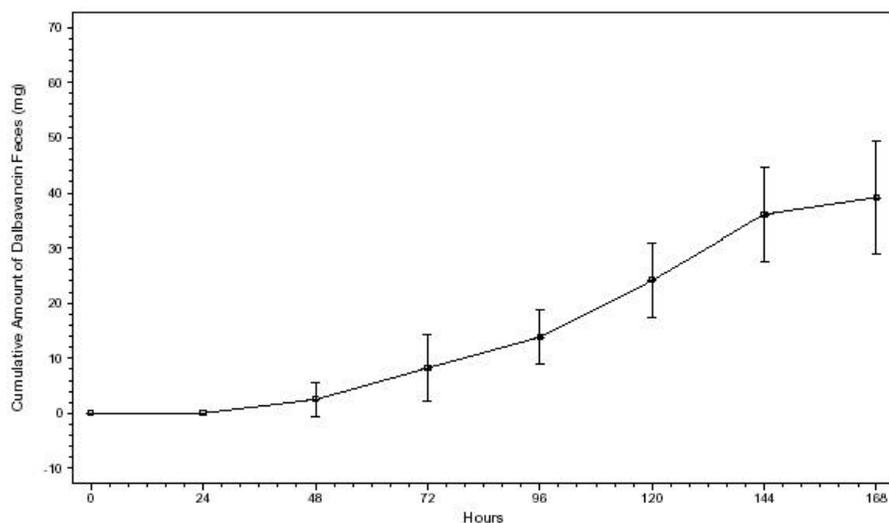
**Figure 18. Mean cumulative amount of dalbavancin and OH-dalbavancin excreted in urine following administration of a single dose of dalbavancin 1000 mg**



In Study VER001-10, the sponsor reported that the cumulative amount of dalbavancin and OH-dalbavancin excreted in urine collected over 1008 hrs (42 days) was 330 mg and 117 mg, respectively. Thus, approximately 33% and 12% of an administered dose was excreted in urine as unchanged dalbavancin and OH-dalbavancin, respectively. Based on the results of the two studies, approximately 29% to 45% of an administered dose of dalbavancin was excreted in urine.

The mean cumulative amount of dalbavancin excreted in feces for 168 hrs is shown in Figure 19. Approximately 39 mg (4% of the administered dose) was recovered in feces after 168 hrs. The estimated fraction of drug excreted in feces was approximately 20% of the administered dose and ranged from 5% to 60%.

**Figure 19. Mean cumulative amount of dalbavancin excreted in feces following administration of a single dose of dalbavancin 1000 mg**



### **2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?**

The mean  $C_{max}$  and AUC of dalbavancin increased proportional to dose following single dose administration of dalbavancin 140 mg to 1120 mg, which encompasses the proposed clinical dose. The mean  $CL_T$  remained constant for all doses between 140 mg and 1120 mg and did not demonstrate dose-dependent changes. The mean  $V_{SS}$  remained relatively constant with increasing dose except for a modest decrease with the highest two doses (840 mg and 1120 mg). The mean  $t_{1/2}$  ranged from 149 hrs to 189 hrs and decreased modestly with the highest doses.

### **2.2.5.9 How do the PK parameters change with time following chronic dosing?**

The proposed dosage regimen of dalbavancin is 1000 mg on day 1 and 500 mg on day 8. Dalbavancin was not dosed for an adequate length of time in any clinical study to reach steady-state following multiple dose administration. Thus, it is not possible to address how PK parameters change with time following chronic dosing. However, administration of a loading dose (300 mg to 1000 mg) followed by once-daily administration of a maintenance dose (30 mg to 100 mg) for 7 days, the mean  $CL_T$  values appeared to be less following a single dose than multiple dose administration. The mean half-life values were similar following single dose and multiple dose administration. The subjects in the study were likely not at steady-state by day 7 and account for the greater  $CL_T$  values following multiple dose administration.

### **2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

The inter-subject variability of  $C_{max}$ , AUC,  $CL_T$ , and  $V_{SS}$  was less than 20% among healthy volunteers. Although the inter-subject variability of the  $t_{1/2}$  was less than 15%, the inter-study variability was noted to be higher. The higher variability may be related to the duration of sample times used to calculate the elimination half-life since dalbavancin appears to be a 3-compartment model drug rather than a 2-compartment model drug.

## **2.3 Intrinsic factors**

### **2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**

The impact of renal impairment and hepatic impairment on the pharmacokinetics of dalbavancin were assessed in four Phase 1 clinical studies. The impact of covariates such as age, gender, weight, body surface area, and race on the pharmacokinetics of dalbavancin was assessed using a population pharmacokinetic analysis from two Phase 2 clinical studies and one Phase 3 clinical study. The impact of individual covariates are discussed below.

### **2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

#### **2.3.2.1 Elderly patients**

In the population pharmacokinetic 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 yrs of age (see Appendix 4.3 Pharmacometric review). No dosage adjustment is recommended for patients solely based on age.

### **2.3.2.2 Pediatric patients. What is the status of pediatric studies and/or any pediatric plan for study?**

The Agency has granted the sponsor a deferral of pediatric studies until December 31, 2009.

(b) (4)



### **2.3.2.3 Gender**

In the population pharmacokinetic analysis, no appreciable changes in plasma clearance, central and peripheral compartments of distribution volume, or inter-compartment clearance were observed between male and female patients (see Appendix 4.3 Pharmacometric review). No dosage adjustment is recommended for patients based on gender.

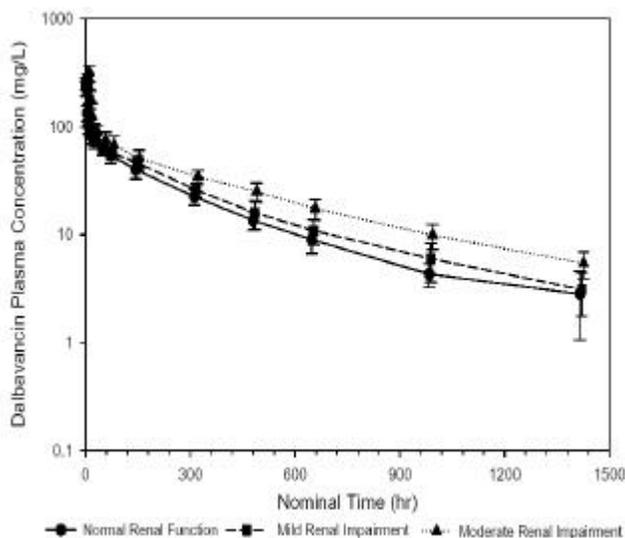
### **2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians**

In the population pharmacokinetic analysis, no appreciable changes in plasma clearance, central and peripheral compartments of distribution volume, or inter-compartment clearance were observed based on race (see Appendix 4.3 Pharmacometric review). No dosage adjustment is recommended for patients based on race.

### **2.3.2.5 Renal impairment**

The impact of mild ( $CL_{CR}$  50-79 mL/min) or moderate ( $CL_{CR}$  30-49 mL/min) renal impairment on the pharmacokinetics of dalbavancin was assessed in Study VER001-13. The mean dalbavancin plasma concentration-time profiles following administration of a single 1000 mg dose of dalbavancin to subjects with normal renal function and mild or moderate renal impairment are shown in Figure 20.

**Figure 20. Mean (SD) dalbavancin plasma concentration-time profiles following administration of 1000 mg dalbavancin in subjects with normal renal function and mild or moderate renal impairment**



The mean plasma pharmacokinetic parameters of dalbavancin are shown in Table 8. The mean  $AUC_{0-\infty}$  increased 10% and 53% in mild and moderate renal impairment, respectively compared to subjects with normal renal function. The dalbavancin mean  $CL_T$  and  $V_{SS}$  decreased as the degree of renal impairment increased. The mean  $CL_T$  was 11% and 35% lower in subjects with mild and moderate renal impairment, respectively compared to subjects with normal renal function. The mean  $V_{SS}$  decreased with increasing renal impairment and was 21% lower for subjects with moderate renal impairment compared to normal renal function. The mean elimination half-life was relatively unchanged across the groups.

**Table 8. Mean ( $\pm$  SD) dalbavancin plasma pharmacokinetic parameter estimates in subjects with normal renal function and mild or moderate renal impairment**

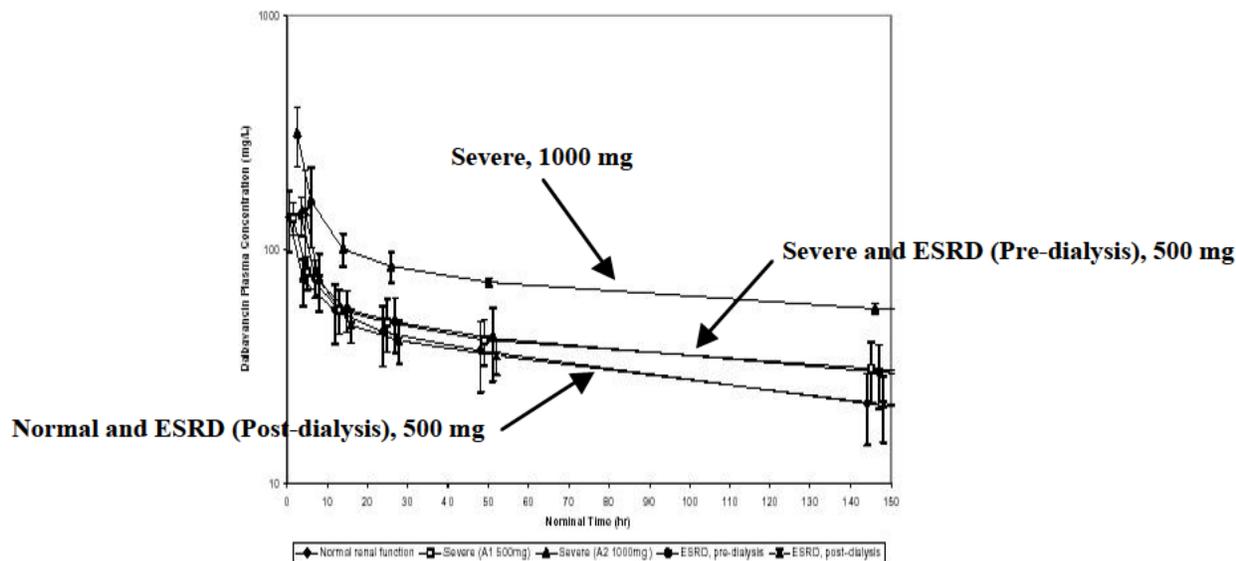
	Group A Normal Renal Function <sup>1</sup> (N = 9)	Group B Mild Renal Impairment <sup>2</sup> (N = 6)	Group C Moderate Renal Impairment <sup>3</sup> (N = 6)
$AUC_{0-\text{day}7}$ ( $\text{hr}^{\cdot}\text{mg/L}$ )	8992 (1362)	9714 (1406)	11050 (2005)
$AUC_{0-\text{day}14}$ ( $\text{hr}^{\cdot}\text{mg/L}$ )	13765 (1986)	15333 (1884)	18060 (3065)
$AUC_{0-\text{inf}}$ ( $\text{hr}^{\cdot}\text{mg/L}$ )	24561 (5252)	27047 (4084)	37665 (7123)
$C_{\text{max}}$ (mg/L)	248.8 (33.0)	266.8 (42.3)	330.7 (55.7)
$T_{\text{max}}$ (hr) <sup>4</sup>	0.50 (Range: 0.42-1.00)	0.50 (Range: 0.50 – 0.55)	0.56 (Range: 0.50 – 1.22)
$V_{\text{SS}}$ (L)	18.5 (3.6)	16.5 (3.3)	14.7 (2.1)
$CL$ (L/hr)	0.0422 (0.0079)	0.0376 (0.0048)	0.0273 (0.0045)
$t_{1/2}$ (hr)	417 <sup>5</sup> (108)	389 (59)	432 (43)

1- $CL_{\text{CR}} > 80$  mL/min; 2- $CL_{\text{CR}}$  50-79 mL/min; 3- $CL_{\text{CR}}$  30-49 mL/min

The sponsor also assessed the pharmacokinetics of dalbavancin in subjects with severe renal impairment ( $CL_{\text{CR}} < 30$  mL/min) and end-stage renal disease (ESRD) immediately before and after 3 hrs of hemodialysis in Study VER001-11. Subjects with normal renal function and ESRD received dalbavancin

500 mg whereas subjects with severe renal impairment received either dalbavancin 500 mg or 1000 mg. The mean dalbavancin plasma concentration-time profiles for all subjects are shown in Figure 21.

**Figure 21. Mean (SD) dalbavancin plasma concentration-time profiles following administration of 500 mg or 1000 mg dalbavancin in subjects with normal renal function, severe renal impairment, or ESRD**



The mean plasma pharmacokinetic parameters for subjects with normal renal function and severe renal impairment or ESRD are shown in Table 9. The mean  $AUC_{0-\infty}$  increased approximately 100% in subjects with severe renal impairment compared to subjects with normal renal function. However, the mean  $AUC_{0-day7}$  and  $AUC_{0-day14}$  increased only 16 % and 31 %, respectively in subjects with severe renal impairment compared to subjects with normal renal function. The mean  $CL_T$  was reduced approximately 50% in subjects with severe renal impairment (500 mg and 1000 mg) whereas the mean  $V_{SS}$  remained constant. The dose-normalized mean  $C_{max}$  was similar in both treatment groups.

**Table 9. Mean (SD) dalbavancin plasma pharmacokinetic parameters for subjects with normal renal function and severe renal impairment or ESRD**

	Severe Renal Impairment <sup>d</sup> (500 mg) Group A1  (N = 6)	Severe Renal Impairment <sup>d</sup> (1000 mg) Group A2  (N = 4)	End Stage Renal Disease (pre-dialysis) (500 mg) Group B1  (N = 3)	End Stage Renal Disease (post-dialysis) (500 mg) Group B2  (N = 3)	Normal Renal Function <sup>b</sup> (500 mg) Group C  (N = 6)
<b>C<sub>max</sub> (mg/L)</b>	136.5 (21.6)	315.3 (89.7)	140.7 (26.4)	145.8 (71.5)	137.3 (39.5)
<b>% CV</b>	15.83	28.46	18.76	49.05	28.78
<b>T<sub>max</sub> (hr)<sup>c</sup></b>	0.54	0.55	0.55	0.58	0.51
<b>Range</b>	(0.50 – 0.65)	(0.50 – 0.60)	(0.50 – 0.62)	(0.50 – 0.65)	(0.50 – 0.52)
<b>AUC<sub>0-day7</sub> (hr*mg/L)</b>	6077 (1392)	10653 (1474)	6069 (1768)	4969 (1153)	5245 (1661)
<b>% CV</b>	22.91	13.84	29.13	23.20	31.68
<b>AUC<sub>0-day14</sub> (hr*mg/L)</b>	10412 (2658)	18698 (1780)	10620 (2881)	8500 (2297)	7971 (2422)
<b>% CV</b>	25.53	9.52	27.13	27.02	30.39
<b>AUC<sub>0-inf</sub> (hr*mg/L)</b>	24074 (6613)	44497 (11483)	19772 (5065)	15587 (6050)	12219 (3298)
<b>% CV</b>	27.47	25.81	25.62	38.81	26.99
<b>V<sub>SS</sub> (L)</b>	13.2 (2.9)	14.2 (0.8)	12.8 (3.4)	14.6 (3.2)	15.0 (4.2)
<b>% CV</b>	21.70	5.62	26.39	22.00	28.22
<b>CL (L/hr)</b>	0.0222 (0.0064)	0.0238 (0.0068)	0.0264 (0.0063)	0.0350 (0.0113)	0.0429 (0.0092)
<b>% CV</b>	28.88	28.73	23.98	32.24	21.37
<b>t<sub>1/2</sub> (hr)</b>	454 (102)	469 (103)	376 (63)	347 (78)	333 (91)
<b>% CV</b>	22.52	21.96	16.83	22.37	27.36

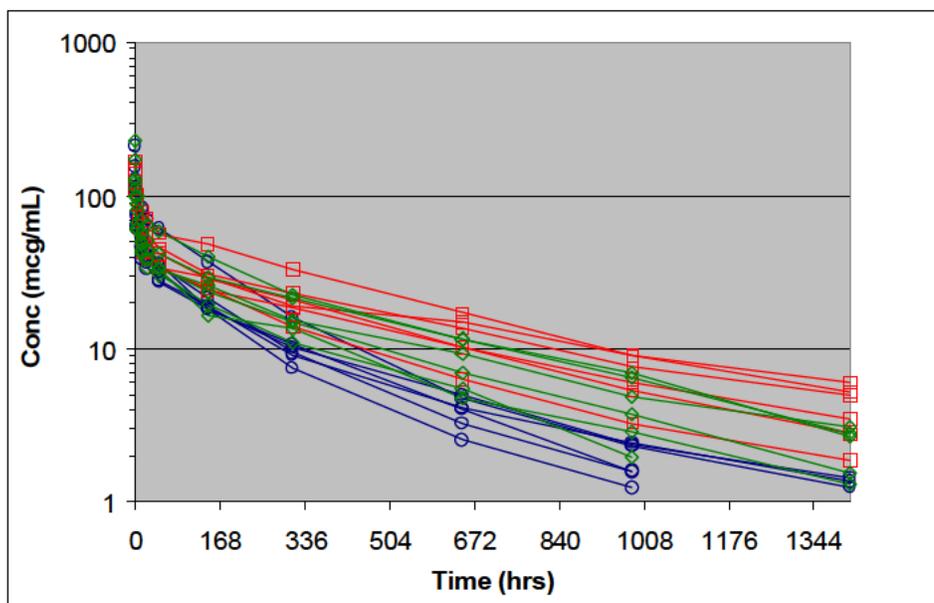
The mean AUC<sub>0-∞</sub> increased 62% and 28% for subjects with ESRD receiving dalbavancin pre-dialysis and post-dialysis, respectively compared to subjects with normal renal function. The mean AUC<sub>0-day7</sub> and AUC<sub>0-day14</sub> for subjects with ESRD were comparable to that for subjects with normal renal function (mean increase of only 5% and 20%, respectively for ESRD subjects combined). The mean CL<sub>T</sub> was reduced 39% compared to subjects with normal renal function when dalbavancin was administered prior to hemodialysis, whereas the mean CL<sub>T</sub> was reduced only 19% when dalbavancin was administered following hemodialysis. The mean C<sub>max</sub> and V<sub>SS</sub> were not altered in subjects with ESRD.

The individual dalbavancin plasma concentrations from subjects with normal renal function and severe renal impairment or ESRD are shown in Figure 22. The mean CL<sub>T</sub> was less among ESRD subjects when dalbavancin was administered immediately prior to hemodialysis rather than following a hemodialysis session. However, the difference among subjects with ESRD may be attributed to the differences in subject weights. ESRD subjects dosed prior to dialysis were mostly female (2 of 3 subjects) with a mean weight of 66.9 kg, while subjects dosed after dialysis were all male (3 of 3 subjects) with a mean weight of 89.2 kg. After correction for body weight, the CL<sub>T</sub> (L/hr/kg) was reduced approximately 20% for both groups of ESRD subjects compared to subjects with normal renal function.

All dialysate samples obtained during hemodialysis were below the LLOQ (1 µg/mL). Since the volume of dialysate during the 3 hr hemodialysis session ranged from 27,500 mL to 28,500 mL, the amount of dalbavancin removed during hemodialysis immediately following administration of the drug was ≤28.5 mg (≤5.7% of the administered dose). Thus, dalbavancin is not appreciably removed from the systemic circulation during hemodialysis.

The concentration of dalbavancin in the venous access lines (blood flow coming from the dialyzer) was 7-18% greater than the concentration of dalbavancin in the arterial access lines (blood flow going toward the dialyzer). While it is possible that the sponsor may have mislabeled blood samples from the arterial and venous access lines, a small amount of drug is likely removed via hemodialysis.

**Figure 22. Mean dalbavancin plasma concentration-time profiles following administration of 500 mg dalbavancin in subjects with normal renal function (blue circles), severe renal impairment (red squares), or ESRD (green diamonds)**



**Dosage Adjustment:**

The protocols of all Phase 2 and Phase 3 clinical studies excluded patients with  $CL_{CR} \leq 50$  mL/min. Thus, no patients with severe renal impairment were intended to be studied and no dosage adjustment was proposed in the clinical studies.

NOTE: Although patients with  $CL_{CR} \leq 50$  mL/min were excluded protocols the Phase 2 and Phase 3 studies, eight patients (with  $CL_{CR}$  30-50 mL/min) were accidentally enrolled and were included in the population PK analysis.

(b) (4)

**Table 10. Mean simulated exposure parameters for subjects with severe renal impairment compared to subjects with normal renal function (performed by sponsor)**

(b) (4)

The reviewer fitted individual concentration-time profiles from subjects with normal renal function and severe renal impairment (Study VER001-11) as well as subjects with normal renal function and mild or moderate renal impairment (Study VER001-13) to a two-compartment open pharmacokinetic model (WinNonlin Professional, Version 4.0, Pharsight Corp., Mountain View CA) with 1/Yhat weighting. Simulations were performed to compare individual concentration-time profiles from subjects with normal renal function (n=15) and mild (n=6) or moderate (n=6) renal impairment receiving 1000 mg dalbavancin on day 1 followed by 500 mg dalbavancin on day 8 (proposed regimen) to subjects with severe renal impairment (n=10) receiving the following dosage regimens: 1000 mg on day 1, 750 mg on day 1 followed by 250 mg on day 8, 750 mg on day 1 followed by 375 mg on day 8, 750 mg on day 1 followed by 500 mg on day 8, 875 mg on day 1 followed by 250 mg on day 8, or 1000 mg on day 1 followed by 250 mg on day 8. The mean pharmacokinetic parameters for each regimen are shown in Table 11. The simulated dalbavancin plasma concentration-time profiles for 750 mg on day 1 followed by either 250 mg, 375 mg, or 500 mg on day 8 are shown in Figures 23-25.

**Table 11. Mean simulated exposure parameters for subjects with severe renal impairment compared to subjects with normal renal function (performed by reviewer)**

Renal function	Dalbavancin regimen	C <sub>max1</sub> (µg/mL)	C <sub>max2</sub> (µg/mL)	AUC <sub>0-168</sub> (µg*hr/mL)	AUC <sub>0-336</sub> (µg*hr/mL)	AUC <sub>0-∞</sub> (µg*hr/mL)
Normal (n=15)	1000 mg/500 mg	254.9	171.9	10,909	22,031	37,111
Mild (n=6)	1000 mg/500 mg	263.0	177.7	10,799	22,321	41,310
Moderate (n=6)	1000 mg/500 mg	336.8	224.0	12,714	26,745	55,791
Severe (n=10)	1000 mg	286.3	NA	13,473	22,378	46,379
	750 mg/250 mg	214.8	118.5	10,105	20,127	46,374
	<b>750 mg/375 mg</b>	<b>214.8</b>	<b>154.3</b>	<b>10,105</b>	<b>21,798</b>	<b>52,169</b>
	750 mg/500 mg	214.8	190.1	10,105	23,470	57,964
	875 mg/250 mg	250.6	126.3	11,789	22,924	52,172
	1000 mg/250 mg	286.3	134.2	13,473	25,721	57,969

C<sub>max1</sub> = peak after first dose; C<sub>max2</sub> = peak after second dose

Of the regimens shown in Table 10 for subjects with severe renal impairment, the 750 mg dalbavancin on day 1 followed by 375 mg on day 8 appears to best match the plasma concentrations of dalbavancin and exposure parameters compared to subjects receiving the proposed dosage regimen (normal renal function and mild or moderate renal impairment). The individual plasma dalbavancin concentrations following administration of 750 mg on day 1 followed by 375 mg on day 8 were within the range of simulated concentrations (throughout the 14-day treatment period) from subjects with normal renal function and mild or moderate renal impairment receiving 1000 mg on day 1 followed by 500 mg on day 8. Thus, the reviewer's recommended dosage regimens of dalbavancin for patients with normal renal function and renal impairment are shown in Table 12.

**Table 12. Sponsor's and reviewer's proposed dosage regimens for patients with normal and impaired renal function**

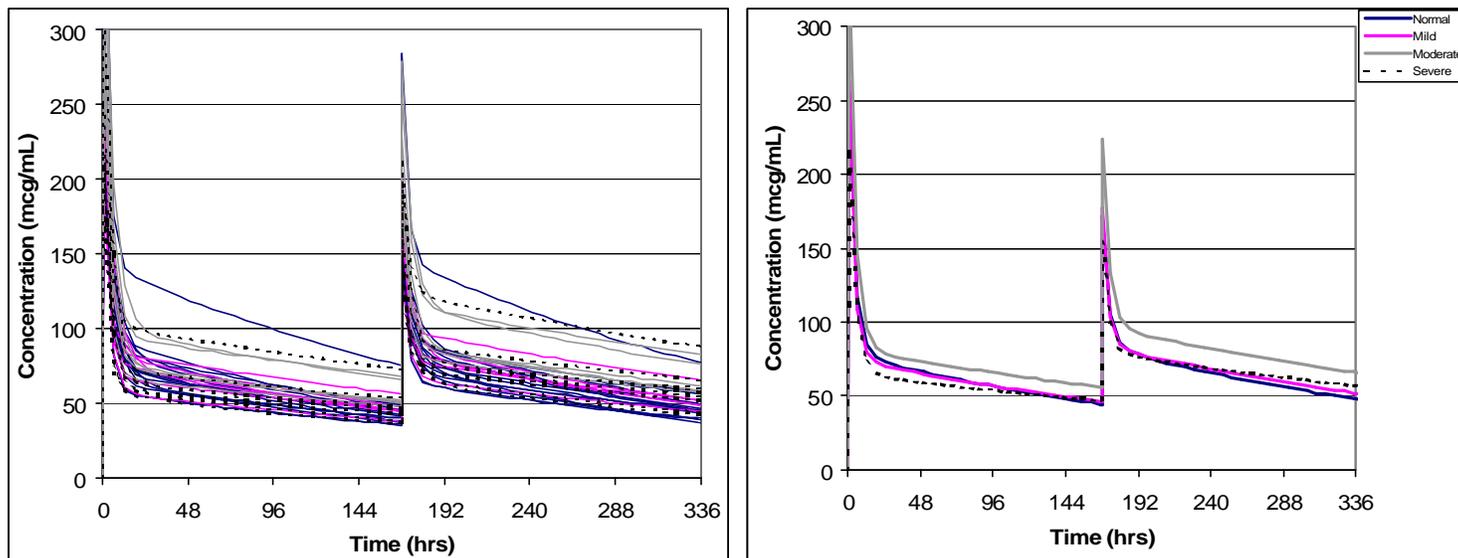
<b>Renal function</b>	<b>Sponsor's proposed regimen</b>	<b>Reviewer's proposed regimen</b>
Normal renal function	1000 mg, then 500 mg	1000 mg, then 500 mg
Mild renal impairment	1000 mg, then 500 mg	1000 mg, then 500 mg
Moderate renal impairment	1000 mg, then 500 mg	1000 mg, then 500 mg
Severe renal impairment	750 mg, then (b) (4)	750 mg, then 375 mg
ESRD receiving HD	1000 mg, then 500 mg	1000 mg, then 500 mg

(b) (4)

(b) (4)

**Figure 24. Simulated individual (left) and mean (right) dalbavancin plasma concentration-time profiles following administration of 1000 mg on day 1 followed by 500 mg on day 8 to subjects with normal renal function (blue lines, n=15), mild renal impairment (red lines, n=6), and moderate renal impairment (gray lines, n=6) and 750 mg on day 1 followed by 375 mg on day 8 to subjects with severe renal impairment (broken lines, n=10)**

**750 mg on day 1 followed by 375 mg on day 8**

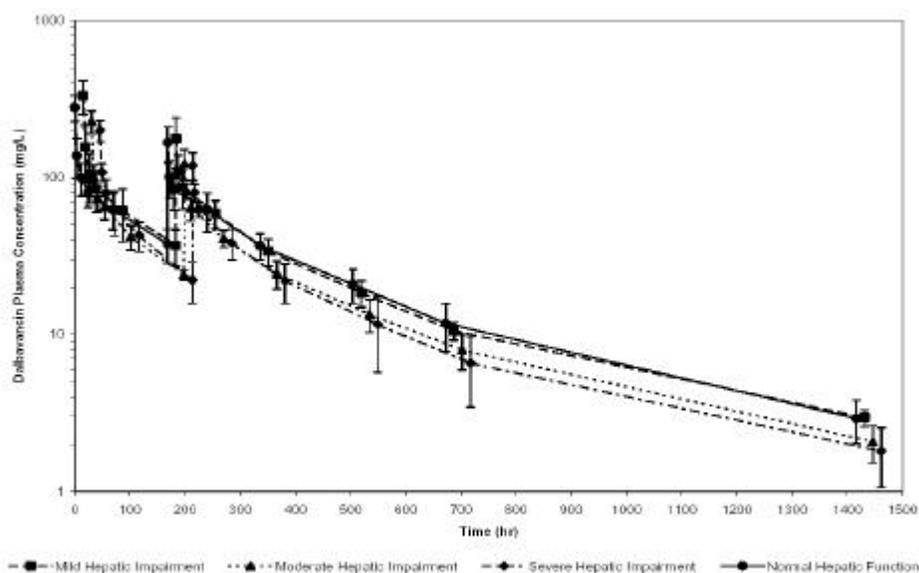


(b) (4)

### 2.3.2.6 Hepatic impairment

The pharmacokinetics of dalbavancin were 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 plasma concentration-time profiles for all subjects following the administration of dalbavancin 1000 mg on day 1, then 500 mg on day 8 infused over 30 min are shown in Figure 26. Mean dalbavancin plasma concentrations were similar among subjects with normal hepatic function and mild hepatic impairment. Although mean dalbavancin plasma concentrations were similar among subjects with moderate and severe hepatic impairment, dalbavancin concentrations were consistently lower than subjects with normal hepatic function.

**Figure 26. Mean (SD) dalbavancin plasma concentration-time profiles following administration of 1000 mg dalbavancin on day 1 and 500 mg on day 8 in subjects with various degrees of hepatic function**



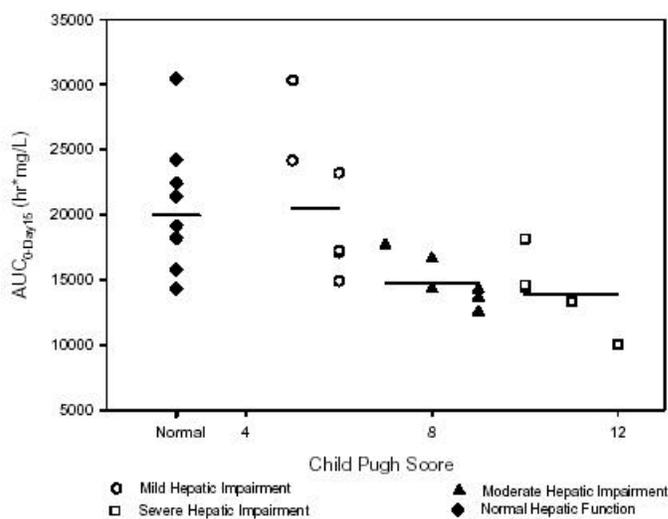
The mean  $C_{max}$  and  $AUC_{0-\infty}$  were similar in subjects with mild hepatic impairment compared to control subjects (Table 13). However, the mean  $C_{max}$  (day 1) and  $AUC_{0-\infty}$  decreased 18% and 30%, respectively in subjects with moderate hepatic impairment and 29% and 36%, respectively in subjects with severe hepatic impairment compared to subjects with normal hepatic function. The mean  $CL_T$  increased 39% and 58% in subjects with moderate and severe hepatic impairment, respectively. The mean elimination half-life of dalbavancin remained unchanged.

**Table 13. Mean (SD) dalbavancin plasma pharmacokinetic parameters**

	Group A Mild Hepatic Impairment <sup>1</sup> (N=6)	Group B Moderate Hepatic Impairment <sup>2</sup> (N=6)	Group C Severe Hepatic Impairment <sup>3</sup> (N=5)	Group D Normal Hepatic Function (N=9)
<b>AUC<sub>0-15d</sub> (hr*mg/L)</b>	11146	7710	7561	10577
SD	3478	1099	1540	2493
%CV	31.21	14.25	20.37	23.57
<b>AUC<sub>0-48h</sub> (hr*mg/L)</b>	21158	14826	14112	20473
SD	5808	1925	2911	4883
%CV	27.45	12.99	20.63	23.85
<b>AUC<sub>0-inf</sub> (hr*mg/L)</b>	33117	23628	21639	33851
SD	6479	3527	5940	8184
%CV	19.57	14.93	27.45	24.18
<b>C<sub>max1</sub> (mg/L)</b>	331.7	227.2	199.0	278.3
SD	80.6	37.5	30.4	52.6
%CV	24.31	16.52	15.25	18.90
<b>C<sub>max2</sub> (mg/L)</b>	177.0	122.7	118.9	166.3
SD	62.4	27.2	23.9	42.9
%CV	35.25	22.18	20.09	25.77
<b>T<sub>max1</sub> (hr)<sup>4</sup></b>	0.53	0.52	0.54	0.52
Range	(0.52-0.55)	(0.52-0.53)	(0.52-0.63)	(0.52-0.53)
<b>T<sub>max2</sub> (hr)<sup>4</sup></b>	168.52	168.51	168.54	168.53
Range	(168.52-168.53)	(168.45-168.52)	(168.52-168.57)	(168.52-168.57)
<b>t<sub>1/2</sub> (hr)</b>	323	320	322	321
SD	27	24	68	24
%CV	8.45	7.34	21.07	7.32
<b>CL (L/hr)</b>	0.0466	0.0647	0.0736	0.0466
SD	0.0084	0.0098	0.0202	0.0110
%CV	17.98	15.22	27.40	23.70
<b>V<sub>ss</sub> (L)</b>	18.1	24.4	25.2	18.3
SD	5.2	3.0	4.0	3.7
%CV	28.65	12.47	15.74	20.19

Although the range of values from individual subjects with hepatic impairment were generally contained with the range of control subjects (Figure 27), the AUC<sub>0-15days</sub> from four of six subjects with moderate hepatic impairment and two of five subjects with severe hepatic impairment were below the range of AUC<sub>0-15days</sub> values from subjects with normal hepatic function. Therefore, caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic insufficiency as no data are available to determine the appropriate dosing.

**Figure 27. Dalbavancin plasma AUC<sub>0-15days</sub> vs. Child Pugh score following administration of 1000 mg dalbavancin on day 1 and 500 mg on day 8 in subjects with various degrees of hepatic function**



Although the protein binding of dalbavancin was not altered in subjects with severe hepatic impairment (see Section 2.2.5.4), serum albumin concentrations decreased and serum bilirubin concentrations increased with increasing hepatic impairment. It is possible that the equilibrium dialysis method overestimated the protein binding of dalbavancin based upon reasons previously stated.

#### **2.3.2.7 What pregnancy and lactation use information is there in the application?**

The sponsor has not studied dalbavancin in patients who were either pregnant or lactating. No data are available to estimate the transfer of dalbavancin in breast milk.

### **2.4. Extrinsic factors**

#### **2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**

The sponsor has assessed the potential of dalbavancin to alter the pharmacokinetics of co-administered drugs and the potential of co-administered drugs to alter the pharmacokinetics of dalbavancin using *in vitro* methods (see Section 2.4.2 Drug-Drug Interactions). The impact of additional extrinsic factors on the pharmacokinetics of dalbavancin has not been assessed.

#### **2.4.2 Drug-Drug interactions**

##### **2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?**

The sponsor assessed the potential of dalbavancin to act as a substrate, inhibitor, and inducer of Cytochrome P450 isoenzymes. Incubation of dalbavancin with human hepatic microsomes, hepatocytes, and kidney microsomes did not result in appreciable loss of parent compound. Dalbavancin did not inhibit the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 using human microsomal enzymes. A study performed with rats to evaluate the potential of dalbavancin to induce hepatic microsomal enzymes found no clinically relevant changes in any P450 isoenzyme in rats receiving dalbavancin (10 mg/kg/day) for 7 days.

##### **2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?**

Based on the *in vitro* metabolism studies, dalbavancin is not a substrate of cytochrome P450 isoenzymes. A minor metabolite of dalbavancin (OH-dalbavancin) has been observed in human urine, whereas the concentration of metabolite in human plasma is below the limits of quantitation (<0.4 µg/mL). Metabolic transformation is due to hydroxylation in the omega-3 position of the C-11 branched side chain (fatty acid side chain) of component B<sub>0</sub>. Approximately 8% to 12% of the administered dose is excreted as OH-dalbavancin in urine. Since the production of OH-dalbavancin was not observed *in vitro* following incubation of dalbavancin in human hepatocytes, liver microsomes, or kidney microsomes, the metabolism of dalbavancin is poorly understood.

##### **2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?**

Based on the *in vitro* metabolism studies, dalbavancin is neither an inhibitor nor inducer of cytochrome P450 isoenzymes.

**2.4.2.4 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?**

The sponsor has not assessed the potential of dalbavancin to act as a substrate and/or inhibitor of P-glycoprotein.

**2.4.2.6 Does the label specify co-administration of another drug and if so, has the interaction potential between these drugs been evaluated?**

The proposed label states that the pharmacokinetics of dalbavancin were not affected when co-administered with medications including acetaminophen, aztreonam, fentanyl, metronidazole, furosemide, proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, lansoprazole), midazolam, and simvastatin. The interaction between dalbavancin and these drugs has been assessed in the population pharmacokinetic analysis.

**2.4.2.7 What other co-medications are likely to be administered to the target patient population?**

In addition to antibiotics with Gram-negative and anaerobic activity, medications that are likely to be administered to the target population consist of all therapeutics used to treat chronic conditions. The impact of co-administered medications with dalbavancin, including concomitant antibiotics was assessed in the population pharmacokinetic analysis (see Section 2.4.2.8).

**2.4.2.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

Based on the results of the *in vitro* drug metabolism studies with human microsomes and hepatocytes, dalbavancin is not a substrate, inhibitor, or inducer of hepatic cytochrome P450 isoenzymes. Thus, the sponsor has not conducted any formal in vivo drug-drug interaction studies with dalbavancin. The impact of co-administered drugs was assessed during the population pharmacokinetic analysis and demonstrated that the pharmacokinetics of dalbavancin were not statistically altered when co-administered with known cytochrome P450 substrates, inhibitors, and inducers.

**2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?**

Dalbavancin and aztreonam were tested alone and in combination against both Gram-positive and Gram-negative bacteria (20 Gram-positive isolates and 12 Gram-negative isolates) to assess any pharmacodynamic drug-drug interactions between the agents. Against Gram-positive organisms, dalbavancin MICs when tested in the presence of aztreonam remained the same or within one dilution of the dalbavancin MIC when tested alone except for one strain of Group B streptococcus (1 of 2 strains), one strain of Viridans Group streptococcus (1 of 2 strains), and 2 of 2 strains of Group A streptococci. The MICs of these isolates decreased at least 3-6 dilutions in the presence of aztreonam compared with dalbavancin tested alone. Against Gram-negative organisms, aztreonam MICs in the presence of dalbavancin remained the same or within 1-2 dilutions of the aztreonam MIC when tested alone. Thus, the dalbavancin does not affect the antibacterial activity of aztreonam and aztreonam does not affect the antibacterial activity of dalbavancin for Staphylococci and Enterococci and may increase the activity of dalbavancin against Group A, Group B, and Viridans Group Streptococci.

**2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?**

There are no unresolved issues related to metabolism, active metabolites, or metabolic drug interactions. The protein binding of dalbavancin may be overestimated based upon reasons stated in Section 2.2.5.4.

**2.5 General Biopharmaceutics**

**2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?**

Not applicable. Dalbavancin is supplied as a lyophilized powder intended to be administered by intravenous infusion.

**2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?**

A consistent formulation of dalbavancin was used across all clinical studies and manufactured as 200 mg and 250 mg vials. A 500 mg vial (b) (4) is proposed for commercial use. A comparison of the clinical study formulation and to-be-marketed formulation is shown in Table 14.

**Table 14. Comparison of dalbavancin for injection formulations**

Ingredient	Quantity per vial			Function
	200 mg vial	250 mg vial	500 mg vial	
Dalbavancin	(b) (4)			Active
Mannitol	(b) (4)			(b) (4)
Lactose	(b) (4)			(b) (4)
Sodium hydroxide or Hydrochloric acid	(b) (4)			(b) (4)
(b) (4)	(b) (4)			(b) (4)

(b) (4)

Dalbavancin was provided in 20 mL single-use vials containing either 200 or 250 mg of dalbavancin. Phase 3 clinical studies VER001-8 and VER001-9 used both 200 mg and 250 mg vials whereas the Phase 3 study VER001-16 used only 250 mg vials. All other Phase 1 and Phase 2 clinical studies used 200 mg vials.

The to-be-marketed formulation of dalbavancin for injection 500 mg vial (b) (4)

(b) (4)

**2.5.2.1 What data support or do not support a waiver of in vivo BE data?**

As per 21 CFR 320.22, the sponsor requests a waiver of the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the drug product in

the 500 mg vial formulation. The sponsor's request for a waiver of in vivo bioavailability or bioequivalence of the 500 mg vial formulation is acceptable based on the following: 1) the drug product is a parenteral solution intended solely for administration by injection, and 2) following reconstitution, dilution, and prior to injection, the 500 mg vial formulation contains the same concentration of active ingredient.

(b) (4)

**2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

Not applicable.

**2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?**

Not applicable.

**2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?**

Not applicable.

**2.5.4 When would a fed BE study be appropriate and was one conducted?**

Not applicable.

**2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?**

Not applicable.

**2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?**

Not applicable.

**2.5.7 If the NDA is for a modified release formulation of an approved immediate produce without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?**

Not applicable.

**2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or *in vivo* data to evaluate BE?**

Not applicable.

**2.5.9 What other significant, unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE need to be addressed?**

Not applicable.

**2.6 ANALYTICAL SECTION**

**2.6.1 How are the active moieties identified and measured in plasma in the clinical pharmacology and biopharmaceutics studies?**

The sponsor used a reverse phase high performance liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) to quantitate concentrations of dalbavancin (specifically B<sub>0</sub> + B<sub>1</sub>) and OH-dalbavancin from plasma, urine, and skin blister fluid. A microbiological assay with *B. subtilis* ATCC 6633 as the indicator organism was used to determine the concentration of dalbavancin in feces.

**2.6.2 Which metabolites have been selected for analysis and why?**

OH-dalbavancin is the primary metabolite of dalbavancin and has been selected for analysis since it is the only quantifiable metabolite of dalbavancin. OH-dalbavancin shows the same spectrum of antibacterial activity as dalbavancin but 2-64 times less activity than dalbavancin with serum-free medium. However, OH-dalbavancin and dalbavancin have similar inhibitory and bactericidal activity in the presence of 30% bovine serum and 50% human serum. The protein binding of OH-dalbavancin in human serum is unknown.

**2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The reported concentrations of dalbavancin (B<sub>0</sub> and B<sub>1</sub> components) and OH-dalbavancin in plasma represent total concentrations. The protein binding of dalbavancin is approximately 93% and is reversibly bound to human plasma proteins, primarily to albumin. The plasma protein binding of dalbavancin is not altered as a function of drug concentration. (b) (4)

Thus, the concentrations of dalbavancin reported in the study reports represent total concentrations.

**2.6.4 What bioanalytical methods are used to assess concentrations?**

See the response for 2.6.1 stated above.

**2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?**

The range of the standard curves depend upon the matrix (i.e., plasma, urine, skin blister fluid, and feces), analyte, and individual study. In plasma, the standard curves ranged from 0.5 to 50 µg/mL, 0.5 to 64 µg/mL, and 1.0 to 128 µg/mL for dalbavancin (B<sub>0</sub> + B<sub>1</sub>) and from 0.5 to 64 µg/mL and 0.4 to 12.8 µg/mL for OH-dalbavancin. Plasma samples were diluted up to 10-fold when the concentration exceeded the upper limit of the standard curve. In urine, the range of the standard curves were the same as plasma for dalbavancin (B<sub>0</sub> + B<sub>1</sub>) and OH-dalbavancin. In skin blister fluid, the standard curve ranged from 1.0 to 128 µg/mL for dalbavancin and 0.4 to 128 µg/mL for OH-dalbavancin. The standard curve for fecal samples ranged from 0.05 to 3.2 µg/mL and was not specific for dalbavancin or OH-dalbavancin.

**2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?**

The lower limit of quantification depended upon the specific assay and ranged from 0.5 to 1.0 µg/mL for dalbavancin and 0.4 to 0.5 µg/mL for OH-dalbavancin in plasma and urine. For skin blister fluid, the LLOQ was 1.0 and 0.4 µg/mL for dalbavancin and OH-dalbavancin, respectively. The upper limit of quantification ranged from 50 to 128 µg/mL for dalbavancin and 12.8 to 64 µg/mL for OH-dalbavancin in plasma and urine. For skin blister fluid, the ULOQ was 128 µg/mL for dalbavancin and OH-dalbavancin, respectively. For feces, the LLOQ was 0.05 µg/mL and the ULOQ was 3.2 µg/mL.

**2.6.4.3 What is the accuracy, precision, and selectivity at these limits?**

The accuracy of dalbavancin and OH-dalbavancin in plasma, urine, and skin blister fluid was 100 ± 15% and the precision ranged from -15% to +15%. Six lots of pooled human plasma and six lots of pooled human urine were used to assess for endogenous interfering substances. Selectivity was not assessed with pooled skin blister fluid.

**2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?**

The stability of dalbavancin in plasma and urine were assessed under various conditions. Dalbavancin was shown to be stable in plasma at room temperature for 18.75 hours and in urine for 24.5 hours. Dalbavancin was stable in both plasma and urine samples undergoing three freeze-thaw cycles and subsequently extended to 6 freeze-thaw cycles. In addition, room temperature stability was demonstrated in extracted plasma sample stored for 56 hrs and extracted urine stored for 41 hrs. Dalbavancin stock solutions in water were stable at 4°C for 135 days. Dalbavancin QC samples stored at -20°C were found to be stable for 56 weeks in plasma and 5 months in urine. Continuation of the long-term stability evaluation showed that dalbavancin was stable at -20°C for at least 948 days in plasma (and 1431 days in urine).

Based on the limited quantity of human skin blister fluid, the sponsor did not assess the stability of dalbavancin in skin blister fluid under various conditions. Dalbavancin was stable in fecal samples after three freeze-thaw cycles, in extracted samples for up to six hrs at room temperature, and in extracted samples maintained at 4°C after for up to six days.

**2.6.4.5 What is the QC sample plan?**

The sponsor's QC sample plan was dependent upon the matrix, analyte, and individual study. For plasma and urine, the sponsor used either three QCs (0.8, 8.0, and 40.0 µg/mL) for dalbavancin, four QCs (0.75,

1.5, 12.0, and 48.0  $\mu\text{g/mL}$ ) for dalbavancin and OH-dalbavancin, or four QCs (3.0, 10, 30  $\mu\text{g/mL}$ , and 100  $\mu\text{g/mL}$ ) for dalbavancin and three QCs (1.0, 3.0, and 10  $\mu\text{g/mL}$ ) for OH-dalbavancin.

The QC sample plan of dalbavancin in skin blister fluid utilized three QCs (3.0, 50, and 100  $\mu\text{g/mL}$ ) for dalbavancin and three QCs (1.2, 5.0, and 10  $\mu\text{g/mL}$ ) for OH-dalbavancin. For the analysis of dalbavancin in fecal samples, the sponsor used three QCs (0.2, 2.0, and 10  $\mu\text{g/mL}$ ). The assay was not specific to quantitate dalbavancin ( $B_0 + B_1$ ) and OH-dalbavancin concentrations.

### **3. DETAILED LABELING RECOMMENDATIONS**

See Appendix 4.1. Proposed Package Insert

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## 4.2 Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

### 4.2.1 *In Vitro* Protein Binding of <sup>14</sup>C-Dalbavancin in Rat, Dog, and Human Plasma (XBL04052\_RPT01092)

#### 2. Introduction

Dalbavancin, a semisynthetic glycopeptide antibiotic, is a mixture of closely related homologues that differ in the structures of the fatty acid side chains of the N-acylaminoglucuronic acid moiety. The major component (b) (4) of dalbavancin is Factor B<sub>0</sub> (hereafter referred to as dalbavancin or parent drug).

The objective of this study was to determine the percent of binding of <sup>14</sup>C-Dalbavancin to proteins in rat, dog, and human plasma. The binding of <sup>14</sup>C-Dalbavancin to the plasma proteins of the rat, dog, and human was determined at multiple concentrations using an equilibrium dialysis method

#### 3. Method

##### 3.1 Preparation of Plasma

To prepare dog plasma, whole blood was centrifuged at 2500 rpm at 4° C for 10 minutes. The resultant dog (beagle, 3 dogs were used) plasma was transferred into clean containers. Rat (Sprague Dawley), and human plasma used in the protein binding study was purchased from (b) (4). All the plasma samples used sodium heparin as anticoagulant.

##### 3.2 Determination of Radioactivity

Radioactivity was measured by counting aliquots directly in a liquid scintillation counter (LSC). Concentration of radioactivity in all samples were determined by counting them in a Beckman LS 6000LL, LS 6000IC, or LS5000TD; and LS 5000-2 liquid scintillation counter for 10 minutes or until the 2-sigma error was less than or equal to 2 %, whichever came first. Quench correction was performed using an external standard method.

##### 3.3 Preparation and Analysis of Stock, Working, and Spiking Solution

Aliquots of the spiking and/or working solutions were spiked into the buffer or plasma to achieve the following final nominal concentrations:

Rat	0.1, 1, 10, 50, 75, 100, 125, 165, 200, and 250 µM
Dog	0.1, 1, 10, 50, 100, and 165 µM
Human	0.1, 1, 10, 50, 100, 165, and 200 µM

In all cases, the volume of the spiking and/or working solutions added to plasma were ~1 % (v/v) of the total sample volume.

### 3.4 Determination of Plasma Protein Binding of <sup>14</sup>C-Dalbavancin

The binding of <sup>14</sup>C-dalbavancin to rat, dog, and human plasma proteins was determined by equilibrium dialysis. The molecular weight cut-off of the dialysis membrane was 10,000.

Aliquots (1-mL) of a spiked plasma sample and buffer (Dulbecco's phosphate buffer solution) were transferred to their respective sides of a dialysis cell. Triplicate preparations were made at each concentration. After mounting the assembled dialysis units onto the drive unit of a Dianorm Equilibrium Dialyzer, dialysis was carried out in a 37 °C incubator for 4 hours with constant rotation. At the end of dialysis, the volume of plasma and PBS compartments was measured and duplicate aliquots of both plasma and PBS was radioassayed by LSC. Experimental recovery for each sample was also determined.

In order to evaluate the recovery in the buffer side after dialysis, the empty cells of the buffer side was rinsed with a mixture of DPBS:DMSO (97:3) and the entire rinsing assayed by LSC at the end of the harvest of some of the rat plasma dialysis samples.

### 3.5 Calculations

#### 3.5.1 Bound to Plasma Protein from Equilibrium Dialysis

$$\% \text{ Bound } (F_b) = [(C_{PI} - C_{PBS}) / C_{PI}] * 100 \%$$

where,

$C_{PI}$  = concentrations of the test article in plasma at the end of dialysis

$C_{PBS}$  = concentrations of the test article in PBS at the end of dialysis

## **4. Results and Discussion**

The final concentrations of <sup>14</sup>C-dalbavancin ranged from 0.1-250 µM in rat plasma, from 0.1-165 µM in dog plasma, and from 0.1-200 µM in human plasma.

The extent of *in vitro* binding of <sup>14</sup>C-dalbavancin to rat, dog, and human plasma protein was determined using an equilibrium dialysis method. Equilibrium dialysis was conducted with <sup>14</sup>C-dalbavancin at a concentration of 0.1, 1, 10, 50, 75, 100, 125, 165, 200, and 250 µM in male rat plasma. The concentrations used for the dog and human plasma were as follows: 0.1, 1, 10, 50, 100, and 165 µM for dog plasma; and 0.1, 1, 10, 50, 100, 165, and 200 µM for human plasma. Table 1 shows the summary of the results. <sup>14</sup>C-dalbavancin binding to rat plasma protein ranged from 93.4-94.6 %, with the average value of 94.2 % over the concentration range of 0.1-250 µM. <sup>14</sup>C-dalbavancin binding to dog plasma protein ranged from 90.4-94.1 %, with the average value of 93.1 % over the concentration range of 0.1-165 µM. <sup>14</sup>C-dalbavancin binding to human plasma protein ranged from 90.3-94.0 %, with the average value of 92.6 % over the concentration range of 0.1-200 µM. The unbound fraction remained constant over the wide range of concentrations. In addition, there were no significant species differences in plasma protein binding of <sup>14</sup>C-dalbavancin.

**Table 1: Summary of Protein Binding of <sup>14</sup>C-Dalbavancin in Rat, Dog, and Human Plasma**

Concentration ( $\mu$ M)	Rat Plasma		Dog Plasma		Human Plasma	
	Average % Bound	RSD <sup>1</sup>	Average % Bound	RSD <sup>1</sup>	Average % Bound	RSD <sup>1</sup>
0.1	94.42	NA	94.07	0.48	90.27	2.69
1	94.40	0.11	90.39	NA	91.63	1.08
10	94.56	0.17	93.70	0.41	94.04	0.29
50	94.19	0.85	92.95	1.87	NA	NA
75	94.30	0.12	NA	NA	NA	NA
100	94.61	0.32	93.67	NA	93.90	0.16
125	93.99	0.03	NA	NA	NA	NA
165	93.36	NA	93.56	0.56	92.37	2.42
200	93.65	0.10	NA	NA	93.36	0.08
250	94.09	0.21	NA	NA	NA	NA
AVG	94.16	0.43	93.06	1.46	92.60	1.58

NA: not applicable.

<sup>1</sup>RSD = relative standard deviation

<sup>2</sup>Average % Bound in the concentration range analyzed.

The results from the recovery analysis demonstrate that the recovered dpm values in the total of four rinsings accounted for no more than 7 % of the total radioactivity recovered in the buffer side of the cell, which accounted for less than 0.3 % of the total dpm (both buffer and plasma sides) recovered. It did not show any significantly higher radioactivity (in terms of percent) remaining in the buffer side of the 250  $\mu$ M set than that of the 0.1  $\mu$ M set, indicating that non-specific binding was not an issue.

## 5. Conclusion

The plasma protein binding of <sup>14</sup>C-dalbavancin was ~93-94 % across all three species, and there was no species difference.

## 4.2.2 Protein Binding of Dalbavancin in Human Plasma Collected from Subjects with Renal or Hepatic Impairment (XBL04057\_RPT01153)

### 2. Introduction

Dalbavancin, a semisynthetic glycopeptide antibiotic, is a mixture of closely related homologues that differ in the structures of the fatty acid side chains of the N-acylaminoglucuronic acid moiety. The major component <sup>(b) (4)</sup> of dalbavancin is Factor B<sub>0</sub> (hereafter referred to as dalbavancin or parent drug).

The objective of this study was to determine the binding of <sup>14</sup>C-Dalbavancin to the plasma proteins of human subjects with normal renal and hepatic function and those with renal or hepatic impairment at multiple concentrations using an equilibrium dialysis method.

### 3. Method

#### 3.1 Preparation of Plasma

Human plasma used in the study was obtained from Vicuron clinical studies VER001-11 and VER001-12. The plasma (collected during clinical studies prior to and after the administration of dalbavancin) was collected from three different groups: a group of subjects with severe renal impairment (VER001-11), a group with normal function (VER001-12) and another group of subjects with severe hepatic impairment (VER001-12).

#### 3.2 Determination of Radioactivity

Radioactivity was measured by counting aliquots directly in a liquid scintillation counter (LSC). Concentration of radioactivity in all samples were determined by counting them in a Beckman LS 6000LL, LS 6000IC, or LS5000TD; and LS 5000-2 liquid scintillation counter for 10 minutes or until the 2-sigma error was less than or equal to 2 %, whichever came first. Quench correction was performed using an external standard method.

#### 3.3 Preparation and Analysis of Stock, Working, and Spiking Solution

Aliquots of the spiking and/or working <sup>14</sup>C-dalbavancin solutions were spiked into the pre-dose plasma to achieve the final nominal concentrations of <sup>14</sup>C-dalbavancin: 1, 10, 50, and 250 μM. In all cases, the volume of the spiking and/or working solutions added to plasma were ~1 % (v/v) of the total sample volume.

#### 3.4 Determination of Plasma Protein Binding of <sup>14</sup>C-Dalbavancin

The binding of <sup>14</sup>C-dalbavancin to human plasma proteins was determined by equilibrium dialysis. The molecular weight cut-off of the dialysis membrane was 10,000.

Aliquots (1-mL) of a spiked plasma sample and buffer (PBS) were transferred to their respective sides of a dialysis cell. Triplicate preparations were made at each concentration. After mounting the assembled dialysis units onto the drive unit of a Dianorm Equilibrium Dialyzer, dialysis was carried out in a 37 °C incubator for 4 hours with constant rotation. At the end of dialysis, the volume of plasma and PBS compartments was measured and duplicate aliquots of both plasma and PBS was radioassayed by LSC. Experimental recovery for each sample was also determined.

The feasibility of using LC-MS/MS to determine plasma protein binding was also examined in the study. In this method proved feasible, post-dose samples were to be used to determine plasma protein binding.

### 3.5 Calculations

#### 3.5.1 Bound to Plasma Protein from Equilibrium Dialysis

$$\% \text{ Bound } (F_b) = [(C_{PI} - C_{PBS}) / C_{PI}] * 100 \%$$

where,

$C_{PI}$  = concentrations of the test article in plasma at the end of dialysis (DPM/mL)

$C_{PBS}$  = concentrations of the test article in PBS at the end of dialysis (DPM/mL)

## **4. Results and Discussion**

The final concentrations of  $^{14}\text{C}$ -dalbavancin ranged from 1-250  $\mu\text{M}$  in human plasma.

The extent of *in vitro* binding of  $^{14}\text{C}$ -dalbavancin to human plasma protein was determined using an equilibrium dialysis method. Equilibrium dialysis was conducted with  $^{14}\text{C}$ -dalbavancin at a concentration of 1, 10, 50, and 250  $\mu\text{M}$ . Table 1 shows the summary of the results. The results showed that the bound fraction remained relatively constant over a wide range of concentrations ranging from ~94 % to ~95 %. In addition, there were no significant differences in the plasma protein binding of  $^{14}\text{C}$ -dalbavancin between the patient groups.

The suitability of the LC-MS/MS method for the analysis of the dialyzates was evaluated. One fortified plasma sample at a level of 50  $\mu\text{M}$  was first dialyzed and the dialyzates (both plasma side and the buffer side) were analyzed by a validated method. The analysis was done during the method validation study. The results indicated that the method was not sensitive enough to accurately determine the concentration of dalbavancin in the buffer side. Therefore, the dialysis of the post-dose samples and LC/MS/MS analysis of their dialyzates was not considered.

**Table 1: Summary of *In-Vitro* Protein Binding of <sup>14</sup>C-Dalbavancin in Human Plasma from Different Groups**

Group ID	Sample ID	Vehicle Conc. (µM)	Avg. % Bound
Normal	HP-1-VER001-12N	1	94.2
	HP-10-VER001-12N	10	94.7
	HP-50-VER001-12N	50	93.8
	HP-250-VER001-12N	250	95.0
Mean			94.4
Renal Impaired	HP-1-VER001-11	1	94.7
	HP-10-VER001-11	10	95.0
	HP-50-VER001-11	50	94.4
	HP-250-VER001-11	250	95.0
Mean			94.8
Hepatic Impaired	HP-1-VER001-12S	1	93.4
	HP-10-VER001-12S	10	94.7
	HP-50-VER001-12S	50	94.3
	HP-250-VER001-12S	250	94.9
Mean			94.3

## 5. Conclusion

There were no differences in <sup>14</sup>C-dalbavancin binding to human plasma protein between healthy subjects and those with renal or hepatic impairment. The results showed that the bound fraction remained relatively constant over a wide range of concentrations. The values ranged from ~93.8 % to ~95 % for the subjects with normal renal and hepatic function, ~94.4 % to ~95.0 % for subjects with severe renal impairment, and 93.4 % to 94.9 % for subjects with severe hepatic impairment over the concentration range of 1 to 250 µM (1.818 to 454.6 mg/L). The mean values for each group were 94.4 %, 94.8 %, and 94.3 % for subjects with normal function, subjects with severe renal impairment, and subjects with severe hepatic impairment, resp

### 4.2.3 In Vitro Study of Dalbavancin as Inhibitor(s) of Human Cytochrome P450 Enzymes (XBL03816\_RPT01032)

#### 2. Introduction

Dalbavancin, a semisynthetic glycopeptide antibiotic, is a mixture of closely related homologues that differ in the structures of the fatty acid side chains of the N-acylaminoglucuronic acid moiety. The major component <sup>(b) (4)</sup> of dalbavancin is Factor B<sub>0</sub> (hereafter referred to as dalbavancin or parent drug).

The objective of this study was to determine the IC<sub>50</sub> and/or inhibitory constants for the evaluation of the ability of dalbavancin at a minimum of three concentrations (0.1, 1, and 20 μM) to inhibit the major P450 isoenzymes in human liver microsomes.

#### 3. Materials

##### 3.1 Marker Substrates, Inhibitors, and Internal Standards

The following compounds were used as marker substrates, inhibitors, or internal standards (IS), and were obtained either from <sup>(b) (4)</sup> chlorzoxazone, diethyldithiocarbamate sodium salt trihydrate, coumarin, 8-methoxypsoralen, diclofenac sodium, sulfaphenazole, 7-ethoxyresorufin, furafylline, bufuralol HCL, quinidine, S-(+)-mephénytoin, tranylcypromine (trans-2-phenylcyclopropylamine) HCL, midazolam HCL, ketoconazole, dextrorphan tartarate, and 4'-hydroxydiclofenac.

#### 4. Test System

Pooled human liver microsomes (HLM) (Lot Nos. 0310091 and 0310156; mixed gender pool of 50 donors) were obtained from <sup>(b) (4)</sup>

#### 5. Methods

##### 5.1 Preparation of Marker Substrate, Inhibitors, and IS Stock Solutions

Stock solutions from 1 to 10 mM were prepared in organic solvents and stored in a freezer at ~-20 °C. Prior to use, the stock solutions were brought to room temperature and vortexed.

##### 5.2 Preparation of Dalbavancin Stock Solution in DMSO (20 mM)

The stock solution was prepared by dissolving 36.44 mg of dalbavancin in 1.0 mL of DMSO. The concentration of the solution was 20 mM (uncorrected for purity). The solution was stored at ~-20 °C.

##### 5.3 Preparation of Dalbavancin Stock Solution in DMSO (20 mM)

Each 20 mg unit of human microsomes (20 mg/mL) was diluted with 3.0 mL of 0.1 M potassium phosphate buffer. (pH 7.4). The microsomal suspensions from more than one tube were combined. The resulting suspension was kept in an ice-water bath at approximately 4 °C until used.

#### 5.4 Preparation of Internal Standard Quenching Solution

A (b) (4) and used to quench all CYP enzyme reactions, except 2E1. A (b) (4) and used to quench the 2E1 reaction.

#### 5.5 Incubation System

##### 5.5.1 Dalbavancin Incubations

The mixture containing isoform specific marker substrates and reagents were prepared in an ice bath. The specified volumes of reagents were added to each of the 96-well plate according to this sequence: mixture, microsomes, dalbavancin. Each incubation was prepared in duplicate. The incubation mixture was pre-incubated for 5 minutes in a 37°C shaking water bath. NADPH was then added to initiate the reaction. Samples were incubated aerobically in a 37 °C shaking water bath for 20 minutes. At 20 minutes, all the reactions (except 2E1) were quenched by adding 5 (b) (4). For 2E1, (b) (4) was obtained. The 96-well plate was placed at ~20 °C for at least one hour. The plate was then centrifuged for 5 minutes at ~4500 rpm. The supernatant was transferred to another 96-well plate (b) (4). The plate was stored at ~-20°C until analyzed by HPLC/MS/MS analysis.

##### 5.5.2 Negative Control 1 (NC1) Incubations

The NC1 samples for each CYP isozyme were incubated in the same manner as the dalbavancin incubation without the addition of dalbavancin.

##### 5.5.3 Negative Control 2 (NC2) Incubations

The NC2 samples for each CYP isozyme were incubated in the same manner as the dalbavancin incubations, without the addition of NADPH or dalbavancin. An equal volume of phosphate buffer was substituted for the NADPH, and DMSO was substituted for the dalbavancin.

##### 5.5.3 Positive Control (PC) Incubations

The positive control samples for each CYP isozyme were incubated in the same manner as the dalbavancin incubations, without the addition of NADPH or dalbavancin. An equal volume of phosphate buffer

##### 5.5.4 Data Generation and Calculation

The software used was provided with the mass spectrometer system (b) (4) to integrate the area under the peak for the metabolite of each cytochrome P450 enzyme and the internal standard, and also to calculate the ratio of the metabolite to the internal standard. Quantitation of the metabolite in the incubations containing the test article was based on the mean response factor (RF) of NC1 as 100 % activity. The data were further analyzed using Microsoft® Excel.

$$RF = \frac{\text{Ratio} \left( \frac{\text{Metabolite Peak Area of NCI incubation}}{\text{IS Peak Area of NCI incubation}} \right)}{100\% \text{ activity}}$$

$$\text{test article (TA) \% of NCI activity} = \frac{\text{Ratio} \left( \frac{\text{Metabolite Peak Area of TA incubation}}{\text{IS Peak Area of TA incubation}} \right)}{RF}$$

## 6. Results and Discussion

### 6.1 Negative Controls

The metabolism of known marker substrate in presence (NC1) and absence (NC2) of NADPH for each cytochrome P450 isozyme was used to confirm the ability of the system to detect P450 activity. NC1 incubations were used as a comparison for the incubations containing dalbavancin and to confirm that marker substrates were metabolized by the microsomes. The NC2 incubations confirmed that the marker substrates were stable under the incubation conditions.

### 6.2 Evaluation of Dalbavancin as an Inhibitor of P450

The amount of metabolites formed in the dalbavancin incubations, under various concentrations of dalbavancin, did not differ from the amount formed in the incubations without dalbavancin. This shows that dalbavancin was not an inhibitor of CYP1A2, 2A6, 2B6, 2C19, 2C9, 2D6, 2E1, and 3A4 under the *in vitro* incubation conditions in this study.

Type of Cytochrome p450 and Enzymatic Reaction	Concentration of Dalbavancin			Mean (±SD)	With Known Inhibitor
	0.1µM	1µM	20µM		
CYP1A2: 1µM 7-Ethoxvresorufin 0-dealkylation	100%	105%	98%	101% (3.6%)	59%
CYP2A6: 2.5µM Coumarin 7-hydroxylation	97%	106%	96%	100% (5.5%)	31%
CYP2B6: 200µM S-(+)-Mephenytoin N-demethylation	103%	100%	92%	98% (5.7%)	110% <sup>a</sup>
CYP2C9: 10µM Diclofenac 4'-hydroxylation	107%	120%	119%	115% (7.2%)	43%
CYP2C19: 50µM S-(+)-Mephenytoin 4'-hydroxylation	114% <sup>b</sup>	100%	90%	101% (12%)	37%
CYP2D6: 5µM Bufuralol 1'-hydroxylation <sup>c</sup>	105%	107% <sup>c</sup>	100%	104% (3.6%)	33%
CYP2E1: 100µM Chlorzoxazone 6-hydroxylation	103%	105%	111%	106% (4.2%)	206% <sup>d</sup>
CYP3A4: 2.5 µM Midazolam 1'-hydroxylation	119%	101%	89%	103% (15%)	57%

a. No know specific inhibitor.

b. Repeated assay result.

c. Repeated assay result with 0.1 µM known inhibitor.

d. Inhibitor was prepared in Phosphate Buffer, while dalbavancin and the NCI incubations were prepared in DMSO. DMSO is a known inhibitor of CYP2E1 hydroxylation. Therefore the known inhibitor incubation appeared to be increased when compared to the suppressed NCI incubation.

e. Single data point used.

## 7. Conclusion

Dalbavancin at 0.1, 1, and 20 µM showed no inhibition of the activity of individual cytochrome P450 enzymes, CYP 1A2, 2A6, 2B6, 2C19, 2C9, 2D6, 2E1, and 3A4 under the *in vitro* incubation conditions in this study. Because there was no inhibition of P-450 enzymes by dalbavancin, the IC<sub>50</sub> values could not be determined.

#### 4.2.4 Investigation of the Metabolism of Dalbavancin by Human Primary Hepatocytes

(b) (4) 012176)

### 2. Introduction

Primary hepatocytes represent the best in vitro experimental model for the evaluation of drug metabolism. Unlike microsomes, intact hepatocytes contain the hepatic-drug metabolism enzymes for both Phase 1 and Phase 2 reactions, retain the biological levels of cofactors needed in enzymatic reaction, and have an intact biomembrane. Hepatocytes in monolayer culture, while generally maintaining good viability over several days have the disadvantage of differential expression and decay in expression of P450 isoforms over time. By contrast, short term incubations of hepatocyte suspensions are an appropriate model system to study the hepatic metabolism of new chemical entities.

This report summarizes the results of an incubation experiment with human hepatocytes for 4 hours that included evaluation of the recovery of dalbavancin from the hepatocyte incubations using 2 different quenching solutions and the viability of the hepatocytes exposed to two different concentrations of dalbavancin.

### 3. Materials and Methods

#### 3.1 Materials

Dalbavancin (BI-397 API, Lot # 025) was supplied by (b) (4)  
Cryopreserved primary human hepatocytes (male donor) were purchased from (b) (4)

#### 3.2 Preparation of Dalbavancin Solutions

Dalbavancin was dissolved in DMSO to prepare stock solutions at concentrations of 2 and 10 mg/mL and stored at -10°C. A 40 µM bufuralol working solution in sHMM was prepared from a methanol stock solution of 40mM bufuralol.

#### 3.3 Preparation of Hepatocyte Suspensions

Cryopreserved human hepatocytes, were quickly thawed in a 37°C water bath. The cell suspension was gradually diluted in cold sHMM. After gentle mixing, hepatocytes were recovered by centrifugation at 50Xg for 5 minutes at 4°C and re-suspended in cold sHMM. Cell viability was assessed by the trypan blue exclusion method. The initial viability for the human hepatocytes was approximately 76 %.

#### 3.3 Incubation of Human Hepatocytes Suspensions with Dalbavancin

During the incubation experiment using human hepatocytes, the suitability of 2 different quenching solutions (b) (4) was evaluated for protein precipitation and extraction of the parent drug. Aliquots of 0.25 mL of the hepatocyte suspensions were incubated in 5 mL sterile polypropylene tubes in a 37°C water-jacketed incubator with 95 % air- 5 % CO<sub>2</sub>. After a 30 min pre-incubation, an equal volume of pre-warmed 8 or 40 µg/mL dalbavancin solution in sHMM was added to each tube, yielding final concentrations of 4 and 20 µg/mL. The incubations were stopped at 0 and 4 hours by the addition of ice-cold quenching solution. Incubation mixtures of dalbavancin containing no hepatocytes (zero-protein reference samples) were also included.

Human hepatocyte incubations with bufuralol (final concentration of 20  $\mu\text{M}$ ) were performed in parallel as positive controls. Bufuralol was used as a positive control since it undergoes Phase I, Phase II, and sequential Phase I-Phase II biotransformation. The triplicate incubations with bufuralol were terminated at 0 and 4 hours by the addition of 0.1 mL of 94 % acetonitrile: acetic acid 6 %, (v/v) as a quenching solution.

#### 4. Sample Analyses and Data Processing

The parent compounds (dalbavancin and bufuralol) as well as Phase I and Phase II bufuralol metabolites were monitored on a (b) (4) LCQ LC/MS/MS instrument on the basis of retention time and m/z values.

The percentage of drug remaining relative to its initial amount, and the relative amount of each metabolite, were calculated based on their peak areas on the LC/MC chromatograms relative to the reference parent compound.

#### 5. Results and Discussion

##### 5.1 Bufuralol Metabolism in Human Hepatocytes

###### 5.1.1 Cell Viability in Incubations with Bufuralol

The viability of human hepatocytes following incubation with bufuralol was assessed by the trypan blue exclusion method. After 4 hours of incubation, the viability was approximately 84 % of the initial viability.

###### 5.1.2 Disappearance of Bufuralol

When bufuralol was incubated with primary human hepatocytes, there was approximately 96 % of the parent compound remaining at the end of the 4-hour incubation period.

###### 5.1.3 Formation of Phase I and Phase II Metabolites

Phase I (hydroxybufuralol [M + 16a] and [M + 16b]) and Phase II metabolites (bufuralol glucuronide: [M + 176a] and [M + 176b]); hydroxybufuralol glucuronide: [M + 192a] were formed. Sequential Phase I-Phase II biotransformation (i.e., hydroxylation of parent bufuralol to hydroxybufuralol, followed by glucuronidation to hydroxybufuralol glucuronide [M + 192a] was detected. These results confirmed that the human hepatocytes used in this experiment were functionally intact and metabolically active.

##### 5.2 Dalbavancin Metabolism in Human Hepatocytes

###### 5.2.1 Cell Viability in Incubations with Dalbavancin

The viability of human hepatocytes incubated with 4  $\mu\text{g/mL}$  or 20  $\mu\text{g/mL}$  dalbavancin was assessed. After 4 hours of incubation with dalbavancin, the cell viability was approximately 87 % and 84 % respectively, of the initial value. There were no apparent, differences in cell viabilities in incubations with dalbavancin compared to incubations with bufuralol, a known non-cytotoxic compound indicating that dalbavancin was not cytotoxic to hepatocytes at the concentrations used.

### 5.2.1 Disappearance of Dalbavancin

Table 1 shows the results of monitoring the loss of dalbavancin (4 and 20 µg/mL) in human hepatocytes.

**Table 1: Dalbavancin Remaining Following Incubations with Human Primary Hepatocytes, Using Two Different Quenching Solutions**

**Acetonitrile (1:1)\***

Dalbavancin Concentration	Incubation Time (hrs)	Incubation Matrix	Dalbavancin Peak Area**	Dalbavancin % Remaining
4 µg/mL	0	Without Cells	147428670	100
	4		158290901	107
	0	With Cells	156502381	100
	4		150879302	105
20 µg/mL	0	Without Cells	691274368	100
	4		726647300	105
	0	With Cells	657818112	100
	4		657080181	100

**94% Acetonitrile 6% Acetic Acid (1:5)\***

Dalbavancin Concentration	Incubation Time (hrs)	Incubation Matrix	Dalbavancin Peak Area**	Dalbavancin % Remaining
4 µg/mL	0	Without Cells	137343256	100
	4		134470488	98
	0	With Cells	146932873	100
	4		145256556	99
20 µg/mL	0	Without Cells	640628062	100
	4		651999866	102
	0	With Cells	707607643	100
	4		717400833	101

\* Quenching solution (amount added [v/v] quenching solution:reaction volume).

\*\* Mean value of triplicate incubation samples.

There was no apparent loss of parent compound at either dalbavancin concentration. Dalbavancin was stable throughout the incubation period in the absence of hepatocytes. The results of this experiment indicated that either quenching solution was appropriate for precipitating cell protein and extracting the parent drug. The results also demonstrated no obvious difference in recovery of parent dalbavancin, between the 2 matrices (culture medium with or without cells), signifying that dalbavancin did not bind to cellular protein to any appreciable degree.

Table 2 shows the results of the time course experiment at 4 and 20 µg/mL of dalbavancin. In this experiment, only acetonitrile quenching solution was used. Despite fluctuations in the % of

dalbavancin remaining at the intermediate time points, dalbavancin appeared to be stable throughout the 4 hour incubation with either medium alone or medium with hepatocytes.

**Table 2: Dalbavancin Remaining Following Time Course Incubations with Human Primary Hepatocytes, Using the Acetonitrile (1:1) Quenching Solution**

Dalbavancin Concentration	Incubation Time (hrs)	Incubation Matrix	Dalbavancin Peak Area*	Dalbavancin % Remaining
4 µg/mL	0	Without Cells	736377	100
	4		793260	108
	0	With Cells	791521	100
	0.5		738528	93
	1		708911	90
	2		733030	93
	4		863313	109
20 µg/mL	0	Without Cells	3772955	100
	4		3878729	103
	0	With Cells	3404604	100
	0.5		2939329	86
	1		3429717	101
	2		3529106	104
	4		3744272	110

% Dalbavancin Remaining = average peak area at 0.5, 1, 2 and 4 hours / average peak area at 0 hrs × 100.

\* Human samples for each time point in triplicate were incubated on January 29, 2002 and then were sent in dry ice to (b) (4) for analysis on February 4, 2002. However, these samples (pool of each time point) were sent back to (b) (4) for analysis of disappearance of the parent by LC/MS again (October 3, 2002).

## 5. Conclusion

The results of this study show no evidence that dalbavancin is metabolized by human hepatocytes. Results also show that dalbavancin apparently has no adverse effect on the viability of the hepatocytes.

#### 4.2.5 Comparative *In Vitro* Metabolism of <sup>14</sup>C-Dalbavancin in Rat, Dog, and Human Hepatocytes (XBL04053\_RPT01078)

##### OBJECTIVES:

The objectives of the study were to determine the *in vitro* biotransformation profiles of <sup>14</sup>C-dalbavancin in hepatocytes from male rats, dogs, and humans, as well as to identify or characterize the prominent metabolites by LC/MS and LC/MS/MS. The study was conducted since a previous study using <sup>3</sup>H-dalbavancin incubated with human hepatocytes demonstrated no metabolic activity.

##### FORMULATION:

Dalbavancin (Lot No. CFQ13124, Specific Activity 27.8 µCi/mg, Radiochemical Purity 92.6%)

##### STUDY DESIGN:

Cryopreserved human hepatocytes were obtained from 4 male subjects and pooled prior to incubation. Cryopreserved rat hepatocytes were obtained from male Sprague-Dawley rats and dog hepatocytes from male beagles.

<sup>14</sup>C-Dalbavancin, at a concentration of ~1 µM or ~10 µM, was incubated separately with human, dog, and rat hepatocytes in a 5% CO<sub>2</sub> and 95% humidity incubator at 37°C. Incubations were carried out in wells containing 1 mL of the incubation mixture with at least 1 × 10<sup>6</sup> viable cells. An additional well was prepared in the same way as the others except that <sup>14</sup>C-dalbavancin was excluded and served as blank control. This well was used to assess the viability. Two additional wells were prepared by mixing <sup>14</sup>C-dalbavancin at a concentration of ~1 µM or ~10 µM in incubation media without hepatocytes and served as a negative control. Finally, two additional wells containing 7-ethoxycoumarin (7-EC) and 7-hydroxycoumarin (7-HC) were prepared separately at a concentration of ~100 µM and served as positive controls. At 0 and 4 hrs, the contents of each duplicate hepatocyte mixture was transferred to a tube containing acetonitrile, vortexed, centrifuged, and frozen prior to analysis by HPLC.

##### RESULTS:

At the completion of the 4 hr incubation, approximately 47%, 49%, and 55% of the cells remained viable for rat, dog, and human hepatocytes, respectively.

After 4 hrs of incubation, 99.68%, 99.52%, and 99.47% of 7-HC and 61.44%, 86.53%, and 92.17% of 7-EC were metabolized by human, dog, and rat hepatocytes, respectively (Table 1). Thus, the hepatocyte preparations used in the study appeared to be enzymatically active.

After 4 hrs of incubation at 37°C, the radioprofile of <sup>14</sup>C-dalbavancin was essentially unchanged except for a slight increase of MAG and the appearance of two minor peaks in comparison to the profile of the <sup>14</sup>C-dalbavancin solution used for the preparation of the incubation mixture. The results indicated a slight degradation of <sup>14</sup>C-dalbavancin under the incubation conditions used.

The 0 and 4-hr incubates with 1 and 10 µM <sup>14</sup>C-dalbavancin were analyzed, except for 0 hr incubates with 10 µM <sup>14</sup>C-dalbavancin in rat and dog hepatocytes. The results indicate that <sup>14</sup>C-dalbavancin was metabolically stable after 4 hrs of incubation at 37°C (Table 2). The only difference in the profiles was the appearance of a minor peak observed in the profiles of the incubates at ~1 µM from both the 0 hr and 4 hr samples. The same peak was also observed in the negative control incubates as a minor component after 4-hr incubation, indicating that the compound is likely an artifact.

**Table 1. Metabolism of 7-ethoxycoumarin (7-EC) and 7-hydroxycoumarin (7-HC) in rat, dog, and human hepatocytes**

Biological Matrix <sup>1</sup>	PC <sup>2</sup>	PA (0 hr) <sup>3</sup>	PA (4 hr) <sup>3</sup>	% Metabolized
HH	7-EC	1171446	451693	61.44
	7-HC	1177907	3736	99.68
DH	7-EC	1470109	198027	86.53
	7-HC	1180727	5679	99.52
RH	7-EC	1800665	140921	92.17
	7-HC	1458601	7711	99.47

<sup>1</sup> 7-Hydroxycoumarin (7-HC, 100 µM) and 7-Ethoxycoumarin (7-EC, 100 µM) were incubated at 37 °C with hepatocytes from each species for 4 hr.

HH = human hepatocyte; DH = dog hepatocyte; RH = rat hepatocyte;

<sup>2</sup> Positive control

<sup>3</sup> PA = Peak area at 323 nm. Average of two injections

**Table 2. Mean percent recovered dalbavancin following a 4 hr incubation with rat, dog, and human hepatocytes**

Sample Matrix	NC1 <sup>1</sup>	1 µM		10 µM	
		0h	4h	0h	4h
RH	100.00	99.15%	97.48%	NA	98.19%
DH	100.00	99.71%	98.01%	NA	99.37%
HH	100.00	98.70%	96.49%	100.96%	102.78%

<sup>1</sup>Negative control with incubation medium without hepatocytes

(4 hr incubation with 10 µM dalbavancin or 4-hr incubation with 1 µM dalbavancin;

Refer to HPLC04053002D02 and HPLC04053005D05)

## CONCLUSIONS:

<sup>14</sup>C-dalbavancin was metabolically stable in pooled rat, dog, and human hepatocytes following 4 hrs of incubation. OH-dalbavancin, a metabolite of dalbavancin identified in clinical studies, was not observed in the hepatocyte incubates. The metabolic stability of <sup>14</sup>C-dalbavancin in rat, dog, and human hepatocytes is consistent with its stability observed in liver microsomes.

#### 4.2.6 Comparative *In Vitro* Metabolism of [<sup>14</sup>C]-Dalbavancin in Rat, Dog, and Human Liver Microsomes (XBL03132\_RPT00988)

### 2. Introduction

The objectives of this study were to determine the *in vitro* biotransformation profiles of [<sup>14</sup>C]-dalbavancin in liver microsomes from male rats, dogs, and humans as well as to identify or characterize the prominent metabolites by LC/MS and LC/MS/MS. A previous study using <sup>3</sup>H-dalbavancin incubated with human hepatocytes demonstrated no metabolic activity.

### 3. Materials and Methods

#### 3.1 Materials

Table 1 shows the description of the test and standard compound.

	Radiolabeled Test Chemical	Standard
Name of the Compound	Dalbavancin	Dalbavancin
Empirical Formula	C <sub>88</sub> H <sub>100</sub> Cl <sub>2</sub> N <sub>10</sub> O <sub>28</sub>	
Molecular Weight	1818.3 (radiolabeled)	1816.7
Lot Numbers	CFQ13124	029
Radiochemical Purity	92.6 % (determined by HPLC by (b) (4))	95.9 % (w/w, calculated on dry basis)
Specific Activity	27.8 µCi/mg	

In addition, a known metabolite in urine (OH-dalbavancin, Lot # 001, 71.4 % w/w) was also provided by the sponsor as a standard.

#### 3.2 Test System

Pooled rat liver microsomes from male Sprague-Dawley rats (RLM, Lot # 031000103; a pool of 15 animals) were obtained from (b) (4). Dog liver microsomes (DLM) from male beagle dogs (Lot # 0310058; a pool of 10 animals), and human liver microsomes (HLM) from male human donors (Lot No. 0210411; a pool of 10 donors) were obtained from (b) (4).

#### 3.3 Incubation System

Each mL of the incubation mixture in 100mM of potassium phosphate buffer (pH 7.4) contained 1 mg of microsomal protein. Various test systems also included [<sup>14</sup>C]-dalbavancin, NADPH, and magnesium chloride at initiation. The final concentrations were: test article, 4 or 20 µM; microsomal proteins, = 1 mg/mL; NADPH, = 3mM; magnesium chloride: 10mM; DMSO: 1 % (v/v). 7-EC (100 µM) was used as the positive control for enzyme activity in the microsomes of all species. Two negative control incubations, one (NC-1) without NADPH and the other (NC-2) using heat-deactivated microsomes (~5 min in boiling water), were prepared to determine the stability of the test article in the incubation mixtures.

## 4. Results and Discussion

### 4.1 Enzymatic Activities in Liver Microsomes

The metabolism of 7-EC was used to determine the enzymatic activities in liver microsomes of the three species. After 4 hr of incubation, > 99 % of 7-EC (100 µM) was metabolized by rat, dog, and human liver microsomes in the presence of 3 mM NADPH. This, the microsomal preparations used in this study were enzymatically active.

### 4.2 Stability of [<sup>14</sup>C]-Dalbavancin in the Incubation System

Radiochemical profiling of two negative control incubations with HLM, one without NADPH (NC1) and the other using heat-treated microsomes (5 minutes in boiling water; NC2), were carried out to determine the stability of the test article. After 4 hr of incubation at 37° C, the radioprofile [<sup>14</sup>C]-Dalbavancin was essentially unchanged when analyzed using HPLC. The results indicate that [<sup>14</sup>C]-dalbavancin was stable after 2 hour of incubation at 37°C under atmospheric air.

### 4.3 Extraction of Incubation Mixtures

Acetonitrile extracted > 95 % of the radioactivity from the microsome incubation mixtures of the three species. The PES (post extraction solids) ranged from 0.06 to 4.68 % of the total recovered radioactivity and were not further analyzed. These data suggest that dalbavancin and /or metabolites were not bound to the microsomal proteins.

### 4.4 Metabolite Profiles in Rat, Dog, and Human Liver Microsomes

The summarized radioprofiles generated by collecting and counting fractions of [<sup>14</sup>C]-dalbavancin after 1 and 4 hour of incubation with rat, dog, and human liver microsomes demonstrated that there were no significant differences in profiles between different intervals, concentrations and species. High radioactivity recoveries (> 95 %) in the extracts from the microsome incubation mixtures, no change in metabolite profiles after incubation with microsomes, and the absence of an OH-dalbavancin metabolite in the incubation mixtures demonstrated that dalbavancin was metabolically stable under the *in vitro* metabolism conditions used for the study.

## 5. Conclusion

- Radioactivity recovered in the extracts from the microsome incubation mixtures were > 95 %.
- [<sup>14</sup>C]-Dalbavancin was metabolically stable in rat, dog, and human liver microsomes.
- Additionally, OH-dalbavancin, a metabolite found in previous *in vivo* studies, was not observed in liver microsome incubates.
- No apparent loss of dalbavancin was observed in the liver microsome incubates.
- The metabolic stability of dalbavancin in microsomal incubations is consistent with its stability in human hepatocytes.

#### 4.2.7 *In Vitro* Metabolism of [<sup>14</sup>C]-Dalbavancin in Human Kidney Microsomes (XBL03818\_RPT01063)

### 2. Introduction

The objectives of this study were to determine the *in vitro* biotransformation profiles of [<sup>14</sup>C]-Dalbavancin in human kidney microsomes, as well as identify or characterize the prominent metabolites by LC/MS and LC/MS/MS. Previous studies using radiolabeled dalbavancin showed that dalbavancin was not metabolized by rat, dog, or human liver microsomes, or human hepatocytes.

### 3. Materials and Methods

#### 3.1 Materials

Table 1 shows the description of the test and standard compound.

	Radiolabeled Test Chemical	Standard
Name of the Compound	Dalbavancin	Dalbavancin
Empirical Formula	C <sub>88</sub> H <sub>100</sub> Cl <sub>2</sub> N <sub>10</sub> O <sub>28</sub>	
Molecular Weight	1818.3 (radiolabeled)	1816.7
Lot Numbers	CFQ13124	029
Radiochemical Purity	92.6 % (determined by HPLC by (b) (4))	82.4 % (w/w, as such)
Specific Activity	27.8 µCi/mg	

In addition, a known metabolite in urine (OH-dalbavancin, Lot # 001, 71.4 % w/w) and mannosyl aglycone (MAG; Lot # 001/AS1) was provided by the sponsor.

#### 3.2 Test System

Pooled human kidney microsomes (HKM< Lot # 0310053; a pool of 2 male and 3 female donors) were obtained from (b) (4)

#### 3.3 Incubation System

Each mL of the incubation mixture in 100mM of potassium phosphate buffer (pH 7.4) contained 2 mg of microsomal protein. Various test systems also included [<sup>14</sup>C]-dalbavancin, NADPH, and magnesium chloride at initiation. The final concentrations of [<sup>14</sup>C]-dalbavancin were 0.1, 1, or 10 µM; microsomal proteins: 2mg/mL; NADPH: ~4.5 mM; magnesium chloride: 10mM; DMSO: 1 % (v/v). Midazolam (100 µM) was used as the positive control for enzyme activity in the microsome. Two negative control incubations, one (NC-1) without NADPH and the other (NC-2) using heat-deactivated microsomes (~5 min in boiling water), were prepared to determine the stability of [<sup>14</sup>C]-dalbavancin in the incubation mixture.

## 4. Results and Discussion

### 4.1 Enzyme Activities in Kidney Microsomes

The metabolism of midazolam was used to determine the enzymatic activities in human kidney microsomes. After 2 hr of incubation, ~14 % of midazolam (100  $\mu$ M) was metabolized by human kidney microsomes in the presence of 4.5 mM NADPH. Table 1 shows the metabolism of midazolam by human kidney microsomes.

**Table 1: Metabolism of Midazolam by Human Kidney Microsomes**

Biological Matrix <sup>1</sup>	Ratio (0 hr) <sup>2</sup>	Ratio (2 hr) <sup>3</sup>	%Metabolized <sup>4</sup>
HKM	98.2458611	84.1518124	14.35%

<sup>1</sup> Midazolam (100  $\mu$ M) was incubated at 37 °C for 2 hrs with human kidney microsomes.

HKM = human kidney microsome

<sup>2</sup> Ratio of peak area response of PC and the peak area response of IS for 0-hr smple.

PC = positive control (midazolam); IS = internal standard (b)(4)

<sup>3</sup> Ratio of peak area response of PC and the peak area response of IS for 2-hr smple.

<sup>4</sup> %Metabolized = 100 x (Ratio at 0-hr)/(Ratio at 2 hr)

### 4.2 Stability of [<sup>14</sup>C]-Dalbavancin in the Incubation System

Radiochemical profiling of two negative control incubations were carried out to determine the stability of [<sup>14</sup>C]-dalbavancin. After 2 hr of incubation at 37°C, the radioprofile of [<sup>14</sup>C]-dalbavancin was essentially unchanged except a slight increase of the early peak (M1, R<sub>t</sub> ~ 3 min) after 2 hour of incubation of the NC1 sample. The HPLC radio-chromatograms of the negative control samples (NC1 and NC2) for HKM sampled at 2 hour indicate that M8C appeared at approximately 2 % in the NC2 extract, but not in the NC1 extract. The same was observed in the HPLC radio-chromatograms of NC2 with rat, dog, and human liver microsomes. The results indicate that [<sup>14</sup>C]-dalbavancin was stable after 2 hour of incubation at 37°C under atmospheric air.

### 4.3 Extraction of Incubation Mixtures

Acetonitrile extracted > 94 % of the radioactivity from the microsome incubation mixtures. The PES (post extraction solids) ranged from 4.10 % to 6.33 % of the total recovered radioactivity, and were not further analyzed. These data suggest that dalbavancin and /or metabolites were not bound to the microsomal proteins.

## 5. Conclusion

Dalbavancin was not metabolized by human kidney microsomes. High radioactivity recoveries (>94 %) in the extracts from the microsome incubation mixtures, no change in metabolite profiles after incubation with microsomes, and the absence of known metabolites in the incubation mixtures demonstrated that dalbavancin was metabolically stable under the *in vitro* metabolism conditions used for the study.

**4.2.8 A phase 1, randomized, placebo-controlled, single and multiple dose, dose-escalation study in healthy volunteers to determine the safety, tolerability, and pharmacokinetics of BI397 (Study VER001-1)**

Dates: August 1999 to November 1999

Clinical site: Simbec Research Ltd, Merthyr Tydfil, Wales, UK

Analytical site: [REDACTED] (b) (4)

**OBJECTIVES:**

The objectives of this study were to 1) establish the safety profile and maximum tolerated dose (MTD) of intravenously administered BI397; 2) to characterize the pharmacokinetics of BI397 following single and multiple intravenous doses; and 3) to establish the dose limiting toxicities (DLTs) of BI397 in healthy volunteers.

**FORMULATIONS:**

BI397 lyophilized powder, 200 mg/vial ( Lot No. 2050-096-149570)

Placebo (mannitol 1% solution for injection, [REDACTED] (b) (4) Lot Nos. 99A28B, 98G28BB, and 99F21BA)

Each vial of BI397 contains 200 mg of BI397, 100 mg mannitol, and HCl/NaOH as necessary for pH adjustment.

**STUDY DESIGN:**

This study was a randomized, placebo-controlled, double-blind, dose-escalation, single- and multiple-dose study. Subjects were randomized in a 3:1 fashion (active:placebo) in blocks of four at each of the selected single- and multiple-dose levels. In the single dose portion of the study, BI397 was administered via intravenous infusion over 30 min at a starting dose of 70 mg. Dose escalation of BI397 was then to proceed to 140, 220, 360, 560, and 900 mg unless dose-limiting toxicities occurred. In the multiple dose portion of the study, BI397 was administered once daily for 7 days via intravenous infusion at a starting dose of 70 mg. Dose escalation of BI397 was then to proceed to 140, 220, 360, 560, and 900 mg. The placebo regimen was composed of a 100 mg/10 mL solution of mannitol for injection administered via intravenous infusion as either a single dose or administered once daily for seven days. Although up to 90 healthy adult volunteers were planned to be enrolled, only 23 healthy male adult volunteers, 18 to 60 yrs of age, were enrolled into the study.

Subjects fasted overnight prior to dosing and for four hours after each IV administration. Standardized meals were allowed 4 hrs after the infusion. Liquids were allowed following the infusion (500 mL for each hour during the first 2 hrs, then ad lib afterwards providing at least 2 L but no more than 3 L were taken over a 24 hr period).

Because BI397 is a new glycopeptide antibiotic, high frequency audiometry testing was included in the safety assessments to monitor potential ototoxicity and a neurological examination was included to test vestibular function.

An evaluation of the bactericidal and bacteriostatic effect of BI397 was performed on selected blood sample aliquots that were available following completion of protocol-defined sample analysis for BI397. This assessment was not planned and was not described in the study protocol.

**Single dose:**

Blood samples for determination of serum BI697 concentrations were obtained at 0 (predose), end of infusion, and 0.25, 0.5, 1, 1.5, 2, 4, 6, 12, 18, and 24 hrs and every 24 hrs following the end of infusion until day 7 and on day 14, 21, and 28. [0, 0.5, 0.75, 1, 1.5, 2, 2.5, 4.5, 6.5, 12.5, 18.5, and 24.5 hrs after the start of infusion]

Urine was collected during the following intervals: Pre-dose, 0-4, 4-8, 8-12, 12-24, 24-36, 36-48 then daily until day 7 and on days 14, 21, and 28.

**Multiple dose:**

Blood samples for determination of serum BI697 concentrations were obtained at 0 (predose), end of infusion, and 0.25, 0.5, 1, 1.5, 2, 4, 6, 12, 18, and 24 hrs on days 1 and day 7. On days 2-6, blood was also collected immediately prior to study drug administration. Blood was also collected on days 8, 9-14, 17, 19, and 28.

Urine was collected at 0-4, 4-8, 8-12, and 12-24 hrs on days 1 and 7 and in the morning (not specified) on days 8, 9-14, 17, 19, 21, and 28.

**BI397 ASSAY METHODOLOGY:**

High performance liquid chromatography with mass spectrometric detection (LC/MS/MS)

Criterion	Plasma	Comments
Concentration range	0.5 to 50 µg/mL	Satisfactory
LLOQ	0.5 µg/mL	Satisfactory
Linearity	Not reported	Unsatisfactory
Accuracy	94.2% to 97.6%	Satisfactory
Precision	5.2% to 10.1%	Satisfactory
Specificity	Acceptable	Satisfactory
Stability	Processed samples at RT, freeze/thaw × 3 cycles	Satisfactory

RT = room temperature

The LC/MS/MS method was validated for determining the concentration of BI397 main component, factor B<sub>0</sub> + B<sub>1</sub>.

**PHARMACOKINETIC ANALYSIS:**

VER001 pharmacokinetic parameters were calculated using WinNonlin-Pro software based on a multi-compartment, non-linear model. Descriptive statistics were used to describe the pharmacokinetic parameters. Pharmacokinetic parameters calculated were the maximum observed plasma concentration (C<sub>max</sub>), time of C<sub>max</sub> (T<sub>max</sub>), area under the concentration-time curve from zero to the last concentration measurement (AUC<sub>0-t</sub>), AUC from zero to infinity (AUC<sub>0-∞</sub>), elimination rate constant (λ<sub>z</sub>), and the terminal elimination half-life (t<sub>1/2</sub>). Concentrations below quantifiable limits (<0.5 µg/ml) were treated as 0.48 µg/ml in the computation of mean plasma concentration values and plasma pharmacokinetic parameters.

**STATISTICAL ANALYSIS:**

BI397 pharmacokinetic parameters were calculated using WinNonlin-Pro based on a multi-compartment, non-linear model. Descriptive statistics (mean, geometric mean and standard deviation) were used for the pharmacokinetic parameters AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, t<sub>1/2</sub>, C<sub>max</sub>, T<sub>max</sub>, and λ<sub>z</sub>. Individual subject serum concentration profiles as well as mean and standard deviation concentration were presented graphically.

**RESULTS:**

Fifteen subjects were randomized to receive a single dose of BI397 or placebo and eight subjects were randomized to multiple-dose treatment of BI397 or placebo. Single dose allocation was as follows: Four subjects received placebo, one each at 70 mg, 140 mg, 220 mg, and 360 mg. Three subjects each received a single dose of 70 mg, 140 mg, and 220 mg of BI397, and two subjects received a single dose of 360 mg of BI397. Multiple dose allocation was as follows: Six subjects received 70 mg of BI397 once daily for 7 days and 2 subjects received the placebo once daily for 7 days. The study was discontinued secondary to presumed ototoxicity and therefore, the remaining single and multiple dose treatment regimens specified in the protocol were not evaluated. The demographics of the 23 subjects who completed the study are shown in Table 1.

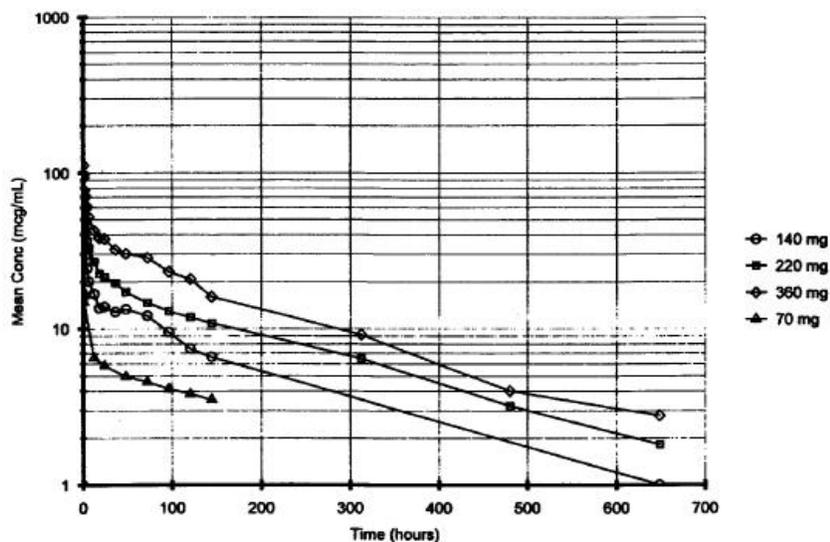
**Table 1. Mean (SD) age, weight, and height of all enrolled subjects**

Demographic	Single Dose				Multiple Dose
	70 mg	140 mg	220 mg	360 mg	70 mg
N	4	4	4	3	8
Age (yrs)	28.8 (10.9)	26.0 (6.7)	33.0 (4.2)	30.3 (6.4)	26.4 (5.3)
Weight (kg)	75.7 (9.6)	72.0 (6.7)	71.3 (2.9)	76.9 (5.7)	74.4 (8.4)
Height (cm)	178.3 (1.7)	174.0 (2.2)	173.3 (4.3)	174.7 (4.7)	175.9 (5.1)

NOTE: Although urine samples were obtained in this study, the collected samples were not assayed and the results of the urine samples are not available.

**Single Dose:**

The mean plasma concentration-time profiles following a single dose of 70, 140, 220 mg, or 360 mg BI397 are shown in Figure 1. The mean (CV%) pharmacokinetic parameters of BI397 following single dose administration are shown in Table 2. The mean  $C_{max}$  increased modestly greater than dose-proportional when normalized by the 70 mg dose and dose proportional when normalized by the 140 mg dose. The mean AUC increased nearly proportional to dose with doses ranging from 70 to 360 mg, whereas the mean  $CL_T$  and  $V_{SS}$  remained relatively constant with increasing dose. In addition, the mean  $CL_T$  of BI397 (0.0381 to 0.0427 L/hr) was less than the predicted creatinine clearance in subjects with normal renal function (7.5 L/hr). The mean  $t_{1/2}$  ranged from 158 hrs (140 mg) to 186 hrs (70 mg) and did not demonstrate a trend with increasing dose.

**Figure 1. Mean plasma BI397 concentration-time profiles following administration of a single dose of BI397**

### Multiple Dose:

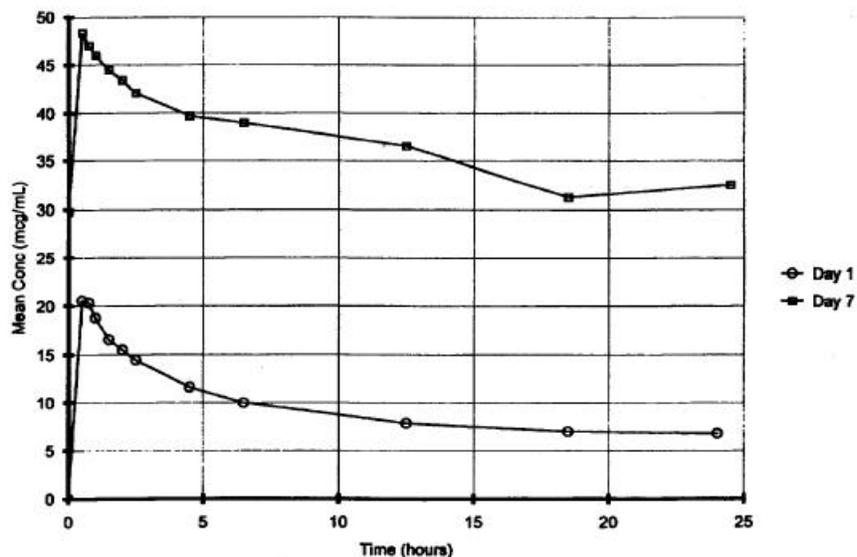
The mean plasma concentration-time profiles of BI397 on day 1 and day 7 following administration of 70 mg BI397 once daily for 7 days are shown in Figure 2. The mean pharmacokinetic parameters following multiple dose administration are shown in Table 2. Accumulation of BI397 was observed after 7 days of once daily dosing as the mean  $C_{max}$  increased 134% (20.75  $\mu\text{g}/\text{mL}$  on day 1 to 48.54  $\mu\text{g}/\text{mL}$  on day 7) and the mean AUC increased 300% (223  $\mu\text{g}\cdot\text{hr}/\text{mL}$  on day 1 to 891  $\mu\text{g}\cdot\text{hr}/\text{mL}$  on day 7). The elimination half-life of BI397 on day 7 was similar to values observed following single dose administration; the estimated elimination half-life on day 1 may not accurately reflect the actual elimination half-life due to the limited sample times. The predicted accumulation factor assuming once daily administration and an elimination half-life of 194 hrs is 12.2 and supports that the plasma concentrations measured on day 7 are not at steady-state.

**Table 2. Mean (CV%) BI397 pharmacokinetic parameters following single dose administration of 70, 140, 220, and 360 mg BI397 and 70 mg daily for 7 days**

Parameter	Single Dose				Multiple Dose (70 mg)	
	70 mg	140 mg	220 mg	360 mg	Day 1	Day 7
$C_{max}$ ( $\mu\text{g}/\text{mL}$ )	17.31 (11%)	44.84 (6%)	70.39 (17%)	111.86 (8%)	20.75 (11%)	48.54 (9%)
$T_{max}$ (hrs)	0.50 (0%)	0.67 (22%)	0.50 (0%)	0.50 (0%)	0.54 (19%)	0.54 (19%)
$AUC^1$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	1679 (18%)	2548 (17%)	5811 (9%)	8735 (5%)	223 (10%)	891 (9%)
$CL_T$ (L/hr)	0.0427 (20%)	0.0403 (18%)	0.0381 (9%)	0.0413 (5%)	---	0.079 (16%)
$V_{SS}$ (L)	11.02 (25%)	7.35 (15%)	8.80 (21%)	9.47 (13%)	---	---
$t_{1/2}$ (hrs)	186 (15%)	158 (19%)	183 (11%)	168 (8%)	61 (34%)	194 (11%)

1- $AUC_{0-\infty}$  following single dose administration;  $AUC_{0-24}$  and  $AUC_{0-t}$  following multiple-dose administration on day 1 and day 7, respectively.

**Figure 2. Mean plasma BI397 concentration-time profiles on day 1 (?) and day 7 (■) following administration of 70 mg once daily for 7 days**



**PHARMACODYNAMICS:**

In addition to the concentration of BI397, remaining plasma samples were evaluated for microbiological activity. For subjects administered single doses of 220 mg and 360 mg, microbiological activity was determined at the end of infusion and at 24 hrs post-infusion. For subjects administered 70 mg daily for seven days, microbiological activity was determined in plasma samples obtained at the end of infusion on day 7 and at 24 hrs post-infusion on Days 1 and 6. Bacteriostatic and bactericidal microbiological activity was determined against two methicillin resistant *Staphylococcus aureus* strains (MRSA 1524 and 453) according to NCCLS procedures. Plasma concentrations of BI397 were determined by the same methodology used for pharmacokinetic drug concentration analysis (LC/MS/MS). The plasma bacteriostatic effect was defined as the highest dilution without visible growth after 24 hrs. The plasma bactericidal effect was defined as the highest dilution of a serum sample that killed 99.9% of the initial inoculum. The MIC and MBC values of the *Staphylococcus aureus* strains in the absence and presence of pooled human serum is shown in Table 3.

**Table 3. MIC and MBC values of BI397 against MRSA 1524 and MRSA 453 with and without 50% pooled human serum**

MRSA Strain	Without pooled human serum		With 50% pooled human serum	
	MIC (mg/mL)	MBC (mg/mL)	MIC (mg/mL)	MBC (mg/mL)
MRSA 1524	≤ 0.13	≤ 0.13	4	4
	≤ 0.13	≤ 0.13	2	2
MRSA 453	≤ 0.13	≤ 0.13	2	2

BI397 exhibited both bacteriostatic and bactericidal activity against MRSA strains 1524 and 453 at dilution factors ranging from <2 to 32. The placebo samples did not show microbiological activity (i.e., the dilution factor was <2). The data demonstrated that bacteriostatic and bactericidal activity could be achieved with BI397 at steady-state plasma concentrations of approximately 20 to 40 µg/mL.

**SAFETY:**

Seven of eleven subjects treated with a single dose of BI397 were reported to have experienced an adverse event. All of these events were reported to be mild in severity. None of the subjects treated with a single dose of placebo reported an adverse event. In the multiple dose group treated with BI397, two of six subjects reported an adverse event, while both subjects treated with multiple dose placebo reported an adverse event.

Subject 42 (70 mg multiple dose) experienced heartburn (not related), injection site erythema (possibly related), and abnormal audiometry findings (possibly related) that were all considered to be mild in severity. Subject 43 (70 mg multiple dose) experienced abnormal audiometry (probably related) that was mild in severity. Both subjects who received placebo reported at least one adverse event. Subject 39 (multiple dose placebo) was reported to have diarrhea (possibly related), a high temperature (possibly related), general aches and pains (possibly related), injection site erythema (possibly related), and abnormal audiometry (possibly related). All of these events were considered to be mild in severity, except diarrhea, which was considered to be moderate in severity. Subject No. 44 (multiple dose placebo) was reported to have injection site erythema (not related), tingling sensation (not related), low frequency abnormal audiometry findings (not related), and high frequency abnormal audiometry findings (possibly related).

The Sponsor conducted a site audit and found inadequate audiology testing facilities, lack of standardized testing methodology, and lack of experience in the conduct of the audiology tests, and, therefore terminated the study. Two audiology experts blindly and independently reviewed the audiology results using the ototoxicity criteria defined by the American Speech-Language-Hearing Association (ASHA)

Guidelines (1994)<sup>2</sup> and their own experienced judgment in assessing whether any subjects experienced ototoxicity. These experts stated that there was no evidence of a systematic pattern of changes across subjects or any apparent correlation to drug administration: that is, single or cumulative dose, single- or multi-dose regimen, or even placebo versus drug. Moreover, results were not consistent with ototoxic change (i.e., bilateral, high frequency, symmetric changes that tend to worsen with increasing frequency). Both experts concluded that the results were consistent with random variability and that the data did not suggest ototoxicity.

**CONCLUSIONS:**

Following single dose administration of BI397 (70 mg to 360 mg), the mean  $C_{max}$  and AUC increased approximately proportion to dose. The mean  $CL_T$ ,  $V_{SS}$ , and elimination half-life remained essentially constant with increasing doses.

Following multiple dose administration (70 mg once daily for 7 days), significant accumulation occurred based on the day 7/day 1  $AUC_{0-24}$  ratio. The mean elimination half-life on day 7 was 194 hrs and was similar to that observed following single doses.

**COMMENTS:**

1. The individual total clearance values for subjects receiving 70 mg once daily for 7 days reported by the sponsor in the electronic data files differed by a factor of 10 compared to the mean total clearance value reported in the study report. The sponsor did not offer any explanation for the discrepancy.

**4.2.9 A phase 1, randomized, placebo-controlled, single and multiple dose, dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous dalbavancin (VER-001, V-Glycopeptide) administered to normal volunteers (Study VER001-2)**

Dates: September 6, 2000 to May 1, 2001

Clinical site: Robert Wood Johnson Medical School Clinical Research Center, New Brunswick, NJ 08903

Analytical site: (b) (4)

**OBJECTIVES:**

The primary objectives of this study were to assess the safety and dose-limiting toxicities (DLTs) associated with dalbavancin, to determine the maximum tolerated dose of dalbavancin, and to characterize the pharmacokinetics of dalbavancin. The secondary objectives of the study were to assess, at each dose level, the serum bactericidal activity at trough, and to evaluate the extent of dalbavancin tissue penetration in specified subjects.

**FORMULATIONS:**

Dalbavancin lyophilized powder, 200 mg/vial (Lot No. 2050-09-149570, API Lot No. 024A, (b) (4))

NOTE: Each vial of dalbavancin contained 200 mg of dalbavancin, (b) (4) of mannitol, HCl and/or NaOH for pH control.

**STUDY DESIGN:**

This was a randomized, double-blind, placebo-controlled, single- and multiple-dose, dose-escalation study designed to assess the safety, pharmacokinetics, and pharmacodynamics of dalbavancin administered IV over 30 min to healthy subjects. Fifty-two subjects 18 to 55 yrs of age were randomized to double-blind treatment with dalbavancin (n=39) or placebo (n=13). Study drug (dalbavancin or placebo) was administered IV once in the single-dose cohort and daily for 7 days in the multiple-dose cohort. In the single-dose cohort, the starting dose was 140 mg followed by 220 mg, 350 mg, 500 mg, 630 mg, 840 mg, and 1120 mg. Dose escalation was to proceed up to 1120 mg or the MTD, whichever was encountered first.

In the multiple-dose phase of the study, dosing consisted of a loading dose (two equal doses given 12 hours apart on day 1) followed by a maintenance dose. The starting regimen was a loading dose of 300 mg (given as 150 mg q12h on day 1) followed by a maintenance dose of 30 mg once daily for six days. Dose escalation was to proceed as follows: 400/40 mg, 600/60 mg, 800/80 mg, 1000/100 mg, or until the MTD was achieved. A minimum of 4 subjects were treated at each single- and multiple-dose level (3 subjects received active drug and 1 subject received placebo). Fasting was not required and there were no dietary restrictions or requirements.

**Single dose:**

Blood samples for determination of plasma dalbavancin concentrations were obtained at 0 (predose), end of infusion (0.5), 1, 2, 4, 6, 12, 18, and 24 hrs after the start of the infusion. In addition, a daily baseline sample was obtained within 30 min of the time of the initial pre-infusion sample taken on day 1.

Urine was collected for 24 hrs on day 1, then a urine sample was collected on days 4, 7, 14, 21, and 28 as near as possible to the time the infusion ended on Day 1.

**Multiple dose:**

Blood samples for determination of plasma dalbavancin concentrations were obtained at pre-infusion, end of infusion (0.5), and 1, 6, 11.5, 12, 12.5, 13, 18 (Day 1), and at 1, 6, 12, and 24 hrs on day 7. On days 2-6, a blood sample was obtained prior to each daily dose (24 hrs after the prior infusion) and then collected a sample at the end of each daily dose infusion. On days 10, 12, 14, 21, 28, and 35, a blood sample was collected within 30 min of the time the infusion started on Day 7/Day 1.

Urine was collected for 24 hrs on days 1 and 7, then a urine sample was collected on days 14, 21, 28, and 35 as near as possible to the time the infusion ended on Day 7.

Serum bacteriostatic and bactericidal activity:

In the single-dose cohort, blood samples were collected prior to drug administration and 24 hrs after the start of the infusion. In the multiple-dose cohort, samples were drawn before the first dose and at 24 and 36 hrs relative to the first dose. Serum samples were tested for bacteriostatic (SBSA) and bactericidal (SBA) activity against *Staphylococcus aureus* 3886 and 3897. SBSA was defined as the highest dilution of a sample that prevented the growth of test organisms. SBA was defined as the highest dilution of a sample that reduced the initial inoculum by 99.9%.

Skin blister fluid:

Cantharadin 0.7% was applied to one forearm of each volunteer in a 1 cm<sup>2</sup> area to induce a blister. Blister fluid aspirates were to be collected at 24 hrs after the start of infusion in the single-dose cohort, and at 24 hrs after the first infusion and 12 hrs post-start of the second infusion in the multiple-dose cohort.

Samples were assayed using the plasma LC/MS/MS standard curve. The results are to be considered only as an estimate because they were quantitated against a plasma standard curve, the concentration was above the limit of quantitation of the assay (no sample remained for dilution and re-analysis), and for one of the samples, the result was generated from a run that failed to meet acceptance criteria.

**DALBAVANCIN ASSAY METHODOLOGY:**

High performance liquid chromatography with mass spectrometric detection (LC/MS/MS)

Criterion	Plasma	Urine	Comments
Concentration range	0.5 to 50 µg/mL	0.5 to 50 µg/mL	Satisfactory
LLOQ	0.5 µg/mL	0.5 µg/mL	Satisfactory
Linearity	R <sup>2</sup> ≥ 0.9952	R <sup>2</sup> ≥ 0.9933	Satisfactory
Accuracy	103.3% to 108.6%	98.9% to 106.4%	Satisfactory
Precision	6.3% to 6.8%	9.7% to 12.6%	Satisfactory
Specificity	Acceptable	Acceptable	Satisfactory
Stability	Note stated	Not stated	Unsatisfactory

RT = room temperature

The analytical procedures specifically measured the combined major components of dalbavancin, B<sub>0</sub> and B<sub>1</sub>. However, the reference standard used to construct a calibration curve and determine the sample concentrations used a purity factor based on the total dalbavancin components. The B<sub>0</sub> and B<sub>1</sub> components represented approximately (b) (4) of the powder used to prepare standards.

**PHARMACOKINETIC ANALYSIS:**

Dalbavancin plasma concentrations were analyzed using a non-compartmental analysis using WinNonlin Standard Version 1.1. Pharmacokinetic parameters were calculated for the maximum observed plasma concentration (C<sub>max</sub>), minimum plasma concentration (C<sub>min</sub>), time of C<sub>max</sub> (T<sub>max</sub>), area under the concentration-time curve from zero to 24 (AUC<sub>0-24</sub>), AUC from zero to infinity (AUC<sub>0-∞</sub>), elimination terminal elimination half-life (t<sub>1/2</sub>), total clearance (CL<sub>T</sub>), renal clearance (CL<sub>R</sub>), apparent volume of

distribution at steady-state ( $V_{SS}$ ), and the percentage of dalbavancin excreted unchanged in the urine (Fe %). At steady-state, the  $CL_T$  was calculated as the maintenance dose/ $AUC_{0-24}$  on day 7. The  $CL_R$  was calculated as the amount of dalbavancin excreted in urine (0-24 hrs) on day 1 or day 7 divided by the  $AUC_{0-24}$  on day 1 or day 7, respectively. The % urinary excretion was calculated as the amount of dalbavancin excreted unchanged into urine (0-24 hrs) on day 1 and day 7 divided by the administered loading dose or maintenance dose, respectively. Summary descriptive statistics were calculated for pharmacokinetic parameters and trough SBA data.

#### STATISTICAL ANALYSIS:

BI397 pharmacokinetic parameters were calculated using WinNonlin-Pro based on a multi-compartment, non-linear model. Descriptive statistics (mean, geometric mean and standard deviation) were used for the pharmacokinetic parameters  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $t_{1/2}$ ,  $C_{max}$ ,  $T_{max}$ , and  $\lambda_z$ . Individual subject serum concentration profiles as well as mean and standard deviation concentration were presented graphically.

#### PHARMACODYNAMIC ANALYSIS:

##### Serum bacteriostatic (SBS) and bactericidal (SBC) titers

Serum samples were tested for bacteriostatic (SBS) and bactericidal (SBC) activity against *Staphylococcus aureus* 3886 and 3897 (methicillin-resistant organisms). In the single-dose cohort, blood samples were collected prior to drug administration and 24 hrs after the start of infusion. In the multiple-dose cohort, samples were drawn before the first dose and at 24 and 36 hrs relative to the first dose. SBS was defined as the highest dilution of a sample that prevented the growth of test organisms. SBC was defined as the highest dilution of a sample that reduced the initial inoculum by 99.9%.

##### Skin blister fluid

Cantharadin 0.7% was applied to one forearm (1 cm<sup>2</sup>) of two subjects to induce a blister. The fluid inside the blister was sampled at 24 hrs after the start of infusion in the single-dose cohort, and at 24 hrs after the first infusion and 12 hrs post-start of the second infusion in the multiple-dose cohort. Samples were assayed by LC/MS/MS. These results are to be considered only as an estimate because they were quantitated against a plasma curve, the concentration was above the limit of quantitation of the assay.

#### RESULTS:

Fifty-two subjects were randomized to receive dalbavancin (n=39) or placebo (n=13) and 51 subjects completed the study. One subject prematurely discontinued at the request of the subject. The demographics of the 52 subjects are shown in Table 1. The single-dose cohort consisted of a higher proportion of female subjects; the multiple-dose cohort consisted of a higher proportion of male subjects. Racial distribution showed more than one-half of subjects to be Caucasian in the single-dose and placebo groups and more than one-half of subjects to be African-Americans in the multiple-dose cohort.

**Table 1. Mean (SD) age, weight, and height of enrolled subjects**

Demographic	Single dose	Multiple dose	Placebo
Gender	8M/13F	10M/8F	7M/6F
Age (yrs)	30.6 (2.2)	25.2 (1.2)	28.1 (2.1)
Weight (kg)	70.1 (2.3)	72.8 (3.3)	71.1 (4.2)
Height (cm)	166.9 (2.0)	170.3 (2.2)	170.4 (2.5)

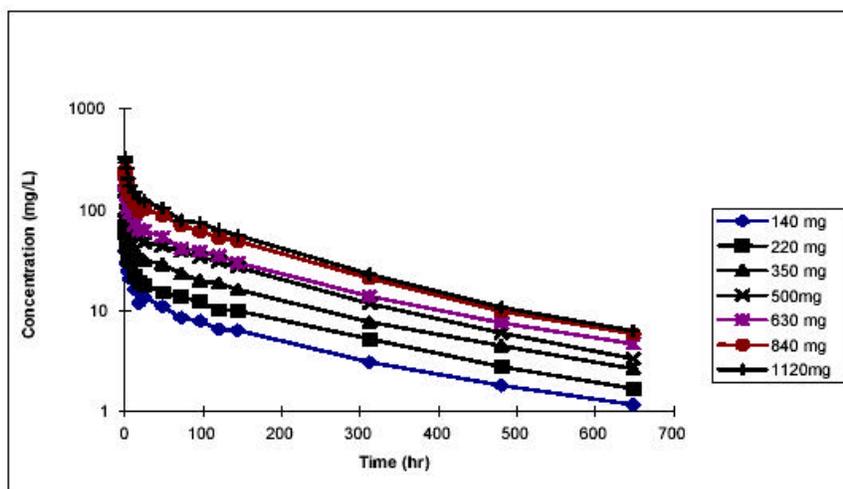
In the single dose cohort, three subjects each received dalbavancin and seven subjects received placebo. In the multiple dose cohort, three subjects each received dalbavancin and six subjects received placebo.

### Single Dose:

The mean plasma concentration-time profiles of dalbavancin following a single dose of 140 mg to 1120 mg are shown in Figure 1. The mean dalbavancin plasma concentrations increased with dose, with measurable concentrations in all dose groups observed through the 648 hr timepoint, or 28 days following the dose.

The mean (CV%) plasma pharmacokinetic parameters of dalbavancin following single dose administration are shown in Table 2. The mean  $C_{max}$  generally occurred at the end of the infusion and increased proportional to dose between 140 mg and 1120 mg. Similarly, the mean AUC increased proportional to dose between 140 mg and 1120 mg. The mean  $CL_T$  remained relatively constant for all doses compared to the 140 mg except the 840 mg dose, in which case it decreased 12% compared to 140 mg. The mean  $V_{SS}$  remained relatively constant with increasing dose for all doses except 500 mg, 840 mg, and 1120 mg. For these three doses, the mean  $V_{SS}$  decreased approximately 20% compared to the 140 mg dose. The mean  $t_{1/2}$  ranged from 149 hrs (1120 mg) to 189 hrs (140 mg) and decreased modestly with the highest doses. The variability among the plasma pharmacokinetic parameters for each dose was generally less than 10%.

**Figure 1. Mean plasma dalbavancin concentration-time profiles following administration of a single dose of dalbavancin 140 mg to 1120 mg**



**Table 2. Mean (CV%) dalbavancin pharmacokinetic parameters following single dose administration of dalbavancin infused over 30 min**

Parameter	140 mg (n=3)	220 mg (n=3)	350 mg (n=3)	500 mg (n=3)	630 mg (n=3)	840 mg (n=3)	1120 mg (n=3)
C <sub>max</sub> (µg/mL)	39.7 (4%)	65.3 (23%)	96.1 (7%)	153 (24%)	190 (31%)	243 (5%)	325 (13%)
T <sub>max</sub> (hrs)	0.667 (43%)	0.5 (0%)	0.5 (0%)	0.5 (0%)	0.833 (35%)	0.5 (0%)	0.5 (0%)
AUC (µg*hr/mL)	3251 (3%)	4955 (11%)	8094 (15%)	12451 (16%)	14758 (27%)	22225 (5%)	25790 (9%)
CL <sub>T</sub> (L/hr)	0.0431 (3%)	0.0448 (12%)	0.0439 (15%)	0.0408 (15%)	0.0446 (24%)	0.0379 (5%)	0.0437 (10%)
V <sub>SS</sub> (L)	10.9 (2%)	11.3 (12%)	10.7 (22%)	8.58 (14%)	10.5 (31%)	7.75 (7%)	8.49 (12%)
t <sub>1/2</sub> (hrs)	189 (2%)	188 (9%)	181 (9%)	159 (3%)	172 (9%)	152 (4%)	149 (2%)
CL <sub>R</sub> (L/hr)	0.0146 (21%)	0.0175 (40%)	0.0148 (20%)	0.0115 (26%)	0.0159 (25%)	0.0130 (15%)	0.0151 (40%)
Urinary excretion on day 1 (% of dose)*	4.47 (11%)	4.91 (35%)	4.45 (10%)	4.11 (11%)	5.03 (34%)	4.56 (9%)	5.27 (41%)

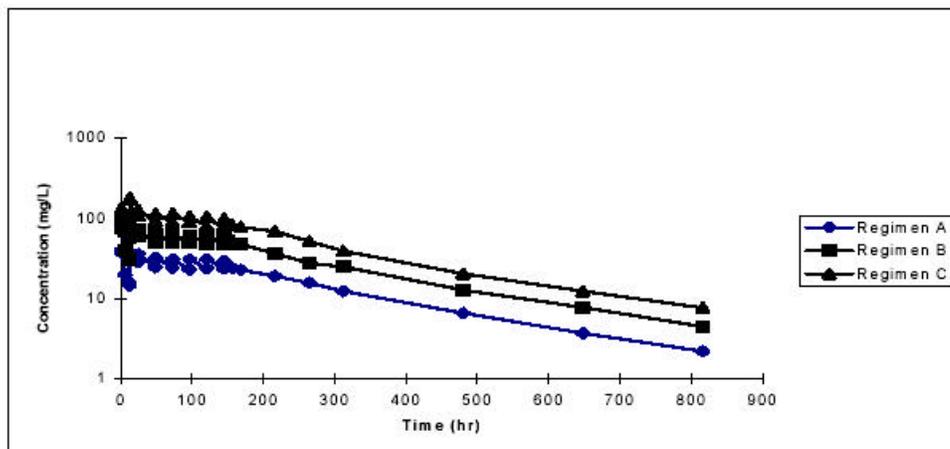
\*based on 24 hr urinary excretion on day 1 divided by the dose

The mean urine concentrations were lower than mean plasma concentrations and did not exceed 20 µg/mL at any time point except for the two highest doses (840 and 1120 mg). The urinary excretion of dalbavancin on Day 1 (24 hr collection) ranged from 4.11% (500 mg) to 5.27% (1120 mg) of the administered dose. The mean urinary clearance of dalbavancin ranged from 0.0115 (500 mg) to 0.0175 (220 mg) L/hr and was substantially less than the mean plasma clearance. The percentage of dalbavancin excreted into urine ranged from 28.1% (500 mg) to 38.4% (220 mg) of the administered dose.

#### Multiple Dose:

The mean plasma concentration-time profiles of dalbavancin 300 mg (day 1)/30 mg (days 2-7), 600 mg (day 1)/60 mg (days 2-7), and 1000 mg (day 1)/100 mg (days 2-7) infused over 30 min are shown in Figure 2. The mean plasma concentration-time profiles of dalbavancin 400 mg (day 1)/40 mg (days 2-7) and 800 mg (day 1)/80 mg (days 2-7) are shown in Figure 3. Overall, the mean plasma concentrations increased with dose. Mean plasma concentrations declined in a log-linear manner from about day 8 or 9 (starting 1 or 2 days following the last dose on day 7) through the last sampling time at 4 weeks following the final dose (840 hrs).

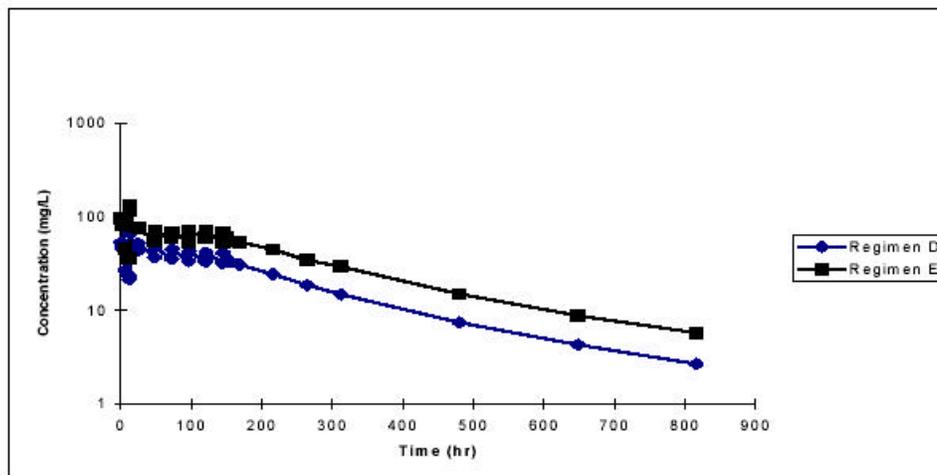
**Figure 2. Mean plasma dalbavancin concentration-time profiles following administration of: regimen A) 300 mg (D1), then 30 mg (D2-D7), Regimen B) 600 mg (D1), 60 mg (D2-D7), Regimen C) 1000 mg (D1), 100 mg (D2-D7)**



The mean (CV%) plasma pharmacokinetic parameters for each group in the multiple-dose cohorts are shown in Table 3. Maximum plasma concentrations on day 1 and 7 were generally observed at the end of infusion (0.5 hrs). The mean  $C_{max}$  and  $C_{min}$  values increased nearly proportional to dose over the range from 300 mg to 1000 mg. The mean  $CL_T$  ranged from 0.0489 L/hr (400/40mg) to 0.0584 L/hr (800/80mg) and was independent of dose. Although the clearance values were greater than observed following single dose administration, it is likely that subjects were not at steady-state by day 7 and may account for the greater values. The mean elimination  $t_{1/2}$  ranged from 184 hrs (400/40mg) to 198 hrs (600/60mg) and showed no trend with increasing dose.

Mean (CV%) urinary pharmacokinetic parameters for the multiple-dose cohort are presented in Table 3. The urinary excretion of dalbavancin into urine on day 7 (24 hr collection) was higher than that observed on Day 1 in single-dose groups and ranged from 25.0% (300/30 mg) to 45.5% (400/40 mg) of the administered maintenance dose.

**Figure 3. Mean plasma dalbavancin concentration-time profiles following administration of: regimen D) 400 mg (D1), then 40 mg (D2-D7), and Regimen E) 800 mg (D1), 80 mg (D2-D7)**



**Table 3. Mean (CV%) dalbavancin pharmacokinetic parameters following multiple dose administration (30 min infusion)**

Parameter	Day	300/30 mg (n=3)	400/40 mg (n=3)	600/60 mg (n=3)	800/80 mg (n=3/2)	1000/100 mg (n=3)
$C_{max1}$ ( $\mu\text{g/mL}$ )	1	57.3 (14%)	77.6 (15%)	115.0 (7%)	131.0 (24%)	180.0 (14%)
$C_{min1}$ ( $\mu\text{g/mL}$ )	1	14.4 (28%)	21.6 (3%)	30.2 (11%)	36.5 (20%)	57.2 (14%)
$C_{max2}$ ( $\mu\text{g/mL}$ )	7	29.6 (18%)	42.3 (18%)	63.7 (5%)	67.7 (3%)	98.9 (19%)
$C_{min2}$ ( $\mu\text{g/mL}$ )	7	22.7 (15%)	30.9 (10%)	47.1 (5%)	54.0 (1%)	77.7 (16%)
AUC ( $\mu\text{g}\cdot\text{hr/mL}$ )	7	597 (13%)	825 (10%)	1221 (6%)	1371 (3%)	1997 (16%)
$CL_T$ (L/hr)	7	0.0508 (13%)	0.0489 (11%)	0.0493 (7%)	0.0584 (3%)	0.0509 (14%)
$t_{1/2}$ (hrs)	7	191 (7%)	184 (9%)	198 (9%)	198 (7%)	189 (6%)
$CL_R$ (L/hr)	7	0.0127 (16%)	0.0228 (48%)	0.0150 (20%)	0.0148 (0%)	0.0189 (26%)
Urinary excretion on day 7 (mg)	7	7.5 (14%)	18.2 (35%)	18.3 (23%)	20.3 (5%)	37.1 (18%)
Urinary excretion on day 7 (%)*	7	25.0 (14%)	45.5 (35%)	30.6 (23%)	25.4 (5%)	37.1 (18%)

\*based on 24 hr urinary excretion on day 7 divided by the maintenance dose

#### PHARMACODYNAMICS:

Corresponding plasma and skin blister fluid samples were obtained from two subjects. The skin blister fluid/plasma concentration ratio was 0.83 for Subject 145 at 24 hrs after administration of 1120 mg single dose. The skin blister fluid/plasma concentration ratio was 0.98 for Subject 322 at 24 hrs after administration of 800 mg in the multiple dose cohort.

**Table 4. Corresponding dalbavancin concentrations obtained from plasma and skin blister fluid from 2 subjects**

Subject	Regimen	Time (hrs)	Plasma (mg/mL)	Blister fluid (mg/mL)	Ratio
145	1120 mg	24 hrs after dose	133	111	0.83
322	800/80 mg	24 hrs after 1st dose	68.9	67.5	0.98

Serum SBC titers from subjects in the single dose and multiple dose cohorts of dalbavancin are shown in Table 5. Samples from subjects who received the lowest single doses (140 and 220 mg) had detectable antimicrobial activity for several days after treatment. In contrast, subjects from the highest single dose groups (840 and 1120 mg) had SBC titers of 16-32 on day 7. Similarly, samples from subjects receiving the two highest multiple-dose regimens (800/80 mg and 1000/100 mg) had SBC titers of >8 for up to 7 days after treatment. Serum samples from subjects treated with placebo had no detectable antimicrobial activity.

**Table 5. Serum bactericidal (SBC) titers on days 2, 3, and 7**

Dose (mg)	Day 2		Day 3		Day 7	
	SBC titer	Conc (mg/mL)	SBC titer	Conc (mg/mL)	SBC titer	Conc (mg/mL)
<b>Single dose</b>						
140	<2-4	13.6	2	10.9	<2	6.35
220	<2-8	17.8	<2-4	15.1	2	9.91
350	2-16	31.3	4-16	28.7	<2-4	16.1
500	8-32	46.9	4-64	43.1	4-16	26.8
630	16-64	61.6	23-68	53.5	4-16	29.7
840	32-64	101	32-64	86.8	16-32	48.5
1120	16-128	122	32-128	103	16-32	55.4
<b>Multiple dose</b>						
300/30	<2-16	28.4	2-16	24.6	2-16	23.7
400/40	8-32	43.4	8-16	36.9	4-16	32
600/60	8-32	61	16-32	50	16-32	46.9
800/80	16-32	75.9	16-32	55	16-32	52.3
1000/100	32-256	107	8-512	92.5	16-512	74.9

**SAFETY:**

Two thirds of all enrolled subjects (67%) reported at least one adverse event (AE). The most prevalent AEs (reported for more than one subject across treatments) in both the single- and multiple-dose cohorts were pyrexia, headache, and nausea. Subjects who received placebo also reported pyrexia (38% of subjects) and headache (31% of subjects) more frequently than other AEs.

Increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in 4 subjects (2 in the 1120 mg dalbavancin group [#143 and #145] and 2 in the placebo cohort [#146 and #324]). Upon questioning by the subinvestigator, Subjects #145, and 146 admitted to alcohol use while on study; these liver function events were not considered by the investigator to be related to dalbavancin.

Two subjects had hyperglycemia that was considered mild and was Grade 1 toxicity; it is not known if the subjects were fasting; both subjects recovered. Subject #310 (400/40 mg) had hyperglycemia on Day 10 that was considered possibly related to study drug. Subject #111 (placebo) had hyperglycemia on Day 4 that was considered probably related to study drug.

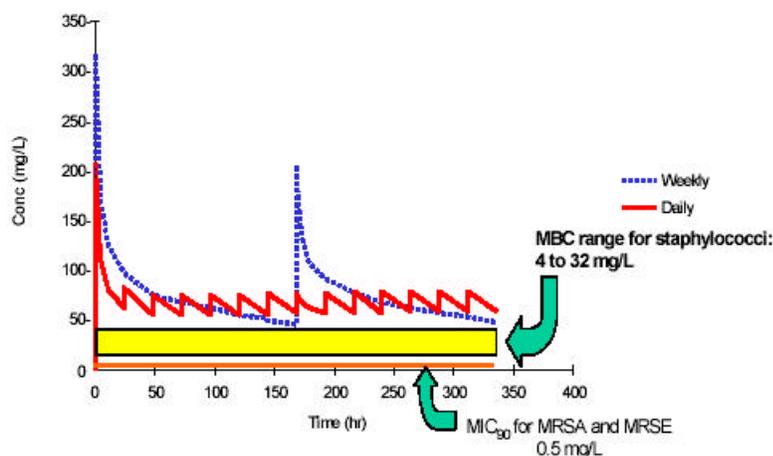
A 12-lead ECG was performed at baseline (Days -7 to -1), Day 3, and Day 7 (multiple-dose cohort only). Only 1 of the 52 subjects had a clinically significant finding. Subject #122 (500 mg single dose group) had an abnormality in V1 and V2 on day 3 that was noted as most likely related to lead placement. No other clinically significant findings were reported.

### CONCLUSIONS:

1. In the single- and multiple-dose cohorts, the dalbavancin mean  $C_{max}$  and AUC increased in proportion to dose while the  $CL_T$  and  $V_{SS}$  remained essentially unchanged, demonstrating linear pharmacokinetics.
2. Low inter-subject variability (<10%) for most of the pharmacokinetic parameters was observed in healthy subjects.
3. Dalbavancin distributes to skin and was present in skin blister fluid; insufficient data were obtained to approximate the percent penetration of dalbavancin into skin blister fluid.
4. Serum bactericidal titers of dalbavancin from the highest doses for the single and multiple dose cohorts support cidal activity as long as 7 days after administration.

### COMMENTS:

Predicted plasma concentrations of dalbavancin following weekly (1000 mg on Day 1, 500 mg on Day 8) and daily (650 mg loading dose, then 65 mg daily dose for 13 additional days) regimens are shown in the figure below. Both regimens of dalbavancin resulted in peak and trough plasma concentrations that remained above the MBC range for methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* for 14 days.



**4.2.10** A Phase I, double blind, placebo controlled study to evaluate the safety, tolerability, and pharmacokinetics of intravenous VER001 (V-glycopeptide) administered to subjects with renal impairment (VER001-3)

#### **Sponsor**

Vicuron Pharmaceuticals  
455, South Gulph Road, Suit 310  
King of Prussia, PA 19406.

#### **Objectives**

The primary objective of the study was to assess the pharmacokinetics of dalbavancin administered intravenously in subjects with mild and moderate renal impairment.

#### **Study Design**

This was a Phase I double blind, placebo controlled, single dose study conducted at a single site in the United States of America. Subjects either received a single 70 mg dose of dalbavancin or matching placebo administered intravenously (IV) as a 30-minute infusion. Blood and urine samples were collected at specific time points over the 4-5 weeks of study participation. Dalbavancin plasma concentrations were assayed using validated liquid chromatography coupled to tandem mass-spectrometry (LC-MS/MS) methods.

#### **Investigational Product(s)**

Single IV infusion of 70 mg dalbavancin on Day 1. The dalbavancin provided was from batch 20381A0, and had a lot number of 2050-09-285048.

#### **Number of Subjects Planned and Enrolled**

Up to 16 subjects with mild to moderate renal impairment were planned. Five subjects were enrolled, 3 received the study drug, 2 received the placebo and all subjects completed the study.

#### **Demographics and Other Baseline Characteristics**

Five subjects (one male and four females) were enrolled in the study. Three subjects were randomized to the dalbavancin treatment group and two subjects received placebo. The ages of the subjects ranged from 31-47 years and the weights ranged from 54.4-99.4 kg. All subjects had mild renal impairment ( $CL_{cr}$  ranged from 54.5-78.2 mL/min).

#### **Pharmacokinetics**

Fig 1 shows the individual plasma concentrations vs time profile after IV administration of a single 70 mg dose of dalbavancin.

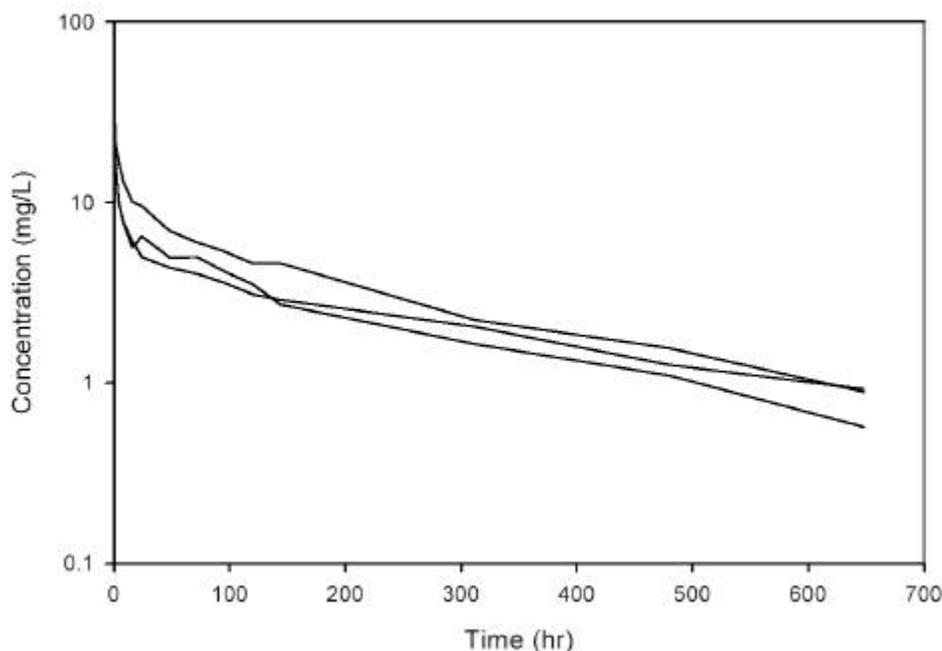
**Fig 1: Individual (n=3) Dalbavancin Plasma Concentrations Versus Time**

Table 1 shows the pharmacokinetic parameters obtained after administration of a single 70 mg IV dose of dalbavancin.

**Table 1: Individual Dalbavancin Pharmacokinetic Parameters for Subjects with Mild Renal Impairment Administered a Single 70 mg Intravenous Dose**

Subject Number	CLcr (mL/min)	Weight (kg)	t <sub>max</sub> (hr)	C <sub>max</sub> (mg/L)	AUC (mg·hr/L)	t <sub>1/2</sub> (hr)	CL (L/hr)	V <sub>ss</sub> (L)
101	54.5	54.9	0.5	29.6	2370	213	0.0295	7.98
103	66.6	93.3	0.5	18.6	1633	229	0.0429	11.1
104	60.6	99.4	0.5	19.0	1908	298	0.0367	14.2
Mean				22.4	1970	247	0.0364	11.1
SD				6.24	373	45	0.007	3.10
%CV				27.8	18.9	18.2	18.4	28.0

**Conclusion**

- In VER001-3, three subjects with mild renal impairment were administered a single IV dose of 70 mg dalbavancin, well below the dosage under study in Phase 2 and 3 patient studies.

- The dose administered in this study was not high enough to provide sufficient data that would allow conclusions to be made concerning renal excretion in patients with mild or moderate renal impairment.
- The study was terminated early because of a sponsor decision to proceed with a higher, more clinically relevant dose.
- Overall, dalbavancin was well tolerated in these three subjects; there were no related AE's or clinically meaningful lab abnormalities.

Reviewer's Comment

*In general, this reviewer agrees with the sponsor's conclusions based on the study results. However, this reviewer does not concur with the conclusion related to safety assessment. The assessment of safety is primarily based on safety data collected after administration of clinically relevant doses. Since the doses used in this study were not clinically relevant, no definitive conclusions (based on the results obtained in this study) can be made regarding the safety of dalbavancin in patients with mild and moderate renal impairment.*

**4.2.11 A phase 1, open label study to evaluate skin tissue penetration and total renal clearance of dalbavancin following administration of a single 1000 mg intravenous dose to healthy volunteers (Study VER001-10)**

Dates: December 27, 2001 to February 21, 2002

Clinical site: Robert Wood Johnson Medical School CRC, New Brunswick, NJ 08903

Analytical site: Vicuron Pharmaceuticals, 21040 Gerenzano (Varese) - Italy

**OBJECTIVES:**

The primary objectives of this study were to determine skin tissue concentrations of dalbavancin and to calculate the extent of renal excretion of dalbavancin. The secondary objective of the study was to correlate skin tissue concentrations with plasma concentrations of dalbavancin.

**FORMULATIONS:**

Dalbavancin lyophilized powder, 200 mg/vial (Lot No. 2050-09-285048, Batch No. 20381A0, (b) (4))

**STUDY DESIGN:**

This was a single dose, open label, two-part study in which up to 12 healthy male and female subjects were to receive 1000 mg of dalbavancin IV infused over 30 min. Subjects could participate in study Part A, study Part B, or both study Parts A and B. Study Parts A and B consisted of the following:

**Part A:** Five skin biopsies with concomitant determination of plasma pharmacokinetics.

**Part B:** Serial 24-hr urine collections for the first seven days while residing in the CRC, then 24-hr urine collections after being re-admitted into the CRC on days 14, 21, 28, and 42.

Six subjects were enrolled, received study drug, participated in both Study Parts A and B, and completed the study. The pharmacokinetic properties of dalbavancin were determined by assessment of plasma, urine, and skin tissue samples.

Blood samples for determination of plasma dalbavancin concentrations were obtained at predose, end of infusion (0.5), 1, 2, 4, 6, 12, 18, and 24 hrs after the start of the infusion. On Days 3 through 6, blood samples were collected each day  $\pm$  60 min relative to the clock time of start of study drug infusion (i.e., 48, 72, 96, 120, 144 hrs). On days 7, 14, 21, 28, and 42, blood samples were collected each day  $\pm$  120 min relative to the clock time of start of study drug infusion (actual times 312, 480, 648, and 984 hrs).

Twenty-four hour collections of voided urine were collected each day beginning on day 1. All voided urine was collected over the 24-48, 48-72, 72-96, 96-120, and 120-144, and 144-168 hr intervals while the subject was confined to the CRC and then 24-hr urine collections after being re-admitted into the CRC on days 14, 21, 28, and 42.

A punch biopsy (5 mm) of skin was removed to obtain a skin sample for drug penetration into skin. A similar biopsy site was used for each biopsy to facilitate biopsies of equivalent thickness. A single skin tissue sample was obtained prior to dosing (Day -14 to -1) and on Days 1 (6-8 hrs post-infusion), 2 ( $\pm$  60 min), 7 ( $\pm$  120 min), and 28 ( $\pm$  1 day). Biopsy sites were limited to torso and legs (above the knee) and arms (above the elbow).

**DALBAVANCIN ASSAY METHODOLOGY:**

High performance liquid chromatography with mass spectrometric detection (LC/MS/MS)

Criterion	Plasma	Urine	Comments
Concentration range	0.5 to 64 µg/mL	0.5 to 64 µg/mL	Satisfactory
LLOQ	0.5 µg/mL	0.5 µg/mL	Satisfactory
Linearity	$R^2 \geq 0.9936$	$R^2 \geq 0.9962$	Satisfactory
Accuracy	88.9% to 103.7%	98.7% to 114.5%	Satisfactory
Precision	4.5% to 6.5%	4.9% to 10.5%	Satisfactory
Specificity	Acceptable	Acceptable	Satisfactory
Stability	Note stated	Not stated	Unsatisfactory

**OH-DALBAVANCIN ASSAY METHODOLOGY:**

High performance liquid chromatography with mass spectrometric detection (LC/MS/MS)

Criterion	Plasma	Urine	Comments
Concentration range	0.5 to 64 µg/mL	0.5 to 64 µg/mL	Satisfactory
LLOQ	0.5 µg/mL	0.5 µg/mL	Satisfactory
Linearity	$R^2 \geq 0.9926$	$R^2 \geq 0.9922$	Satisfactory
Accuracy	93.3% to 115.6%	98.7% to 110.5%	Satisfactory
Precision	5.7% to 8.1%	5.5% to 10.0%	Satisfactory
Specificity	Acceptable	Acceptable	Satisfactory
Stability	Note stated	Not stated	Unsatisfactory

**PHARMACOKINETIC ANALYSIS:**

Dalbavancin and OH-dalbavancin pharmacokinetic parameters were estimated by non-compartmental methods using WinNonlin™ (Pharsight Corporation). The maximum plasma concentration ( $C_{max}$ ) was obtained directly from the observed data. The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule. Plasma clearance ( $CL_T$ ) was computed as dose/AUC. The elimination half-life ( $t_{1/2}$ ) was estimated by linear regression of the log-linear portion of the log concentration-time curve. The apparent volume of distribution at steady state ( $V_{SS}$ ) was calculated from the area under the first moment curve (AUMC) multiplied by the dose and divided by AUC squared. The cumulative amount of dalbavancin excreted in urine was determined as the integrand of the area under the urine excretion curve (AURC). The renal clearance ( $CL_R$ ) was calculated as the ratio:  $CL_R = AURC/AUC$ . The penetration of dalbavancin into blister fluid was determined as the ratio of  $AUC_{skin}/AUC_{plasma}$ .

**STATISTICAL ANALYSIS:**

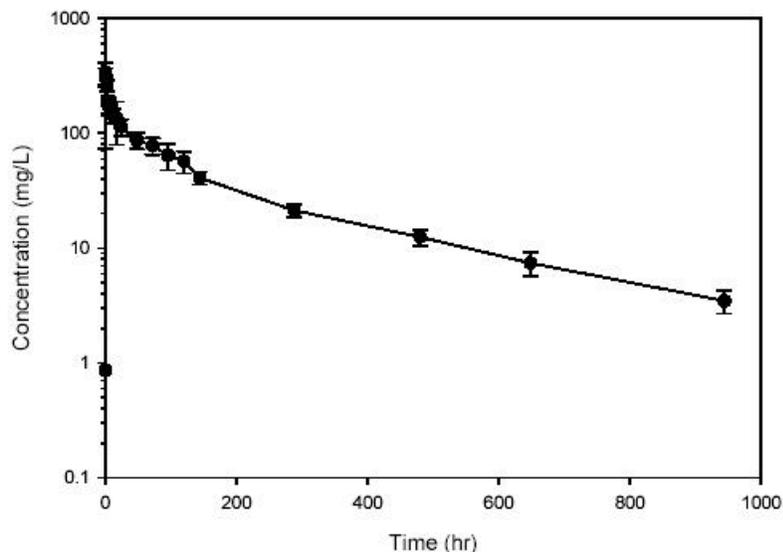
Descriptive statistics were used to analyze the pharmacokinetic parameters.

**RESULTS:**

Six subjects were enrolled, received study medication, and completed the study. The mean (SD) age, height, and weight were 29.8 (8.5) yrs, 174.2 (11.4) cm, and 81.5 (16.9) kg, respectively. One subject was female, five subjects were male, half the subjects were African-American, and the other half were Caucasian.

The mean plasma concentration-time profile of dalbavancin following a single dose of 1000 mg infused over 30 min is shown in Figure 1. Maximum plasma concentrations ( $C_{max}$ ) were reached at the end of infusion and the mean  $C_{max}$  was 340 µg/mL.

**Figure 1. Mean plasma dalbavancin concentration-time profile following administration of a single dose of dalbavancin 1000 mg**



The mean (CV%) plasma and urine pharmacokinetic parameters of dalbavancin following single dose administration are shown in Table 2. The mean  $C_{max}$ , AUC,  $CL_T$ ,  $V_{SS}$ , and  $CL_R$  were within the range of mean values reported in Study VER001-2. However, the mean elimination half-life from the current study (261 hrs) is appreciably longer than the range of values reported in Study VER001-2 (149 to 189 hrs).

**Table 2. Mean (CV%) dalbavancin and OH-dalbavancin pharmacokinetic parameters following a single 1000 mg dose of dalbavancin infused over 30 min**

Parameter	Dalbavancin	OH-Dalbavancin
$C_{max}$ ( $\mu\text{g/mL}$ )	340 (20%)	BLOQ
AUC ( $\mu\text{g}\cdot\text{hr/mL}$ )	24,453 (15%)	BLOQ
$CL_T$ (L/hr)	0.0417 (15%)	BLOQ
$V_{SS}$ (L)	11.2 (11%)	BLOQ
$t_{1/2}$ (hrs)	261 (14%)	BLOQ
$CL_R$ (L/hr)	0.0138 (20%)	BLOQ
Urinary excretion in 24 hrs (mg)	42.6	5.31
Urinary excretion in 168 hrs (mg)	175.3	58.5
Urinary excretion extrapolated to 1008 hrs (mg)	330	117

The sponsor did not state which AUC value was reported (i.e.,  $AUC_{0-984}$ ,  $AUC_{0-\infty}$ ) and the calculation of percent renal excretion using the AURC was not explained. The sponsor calculated the percent urinary excretion using the AURC since urine was collected during the first seven days and then only on days 14, 21, 28, and 42 when subjects were re-admitted to the CRC. The mean urinary excretion of dalbavancin and OH-dalbavancin base solely on urine actually collected was 187.5 mg and 63.0 mg, respectively.

The reviewer calculated the mean  $AUC_{0-984}$ ,  $t_{1/2}$ , terminal trapezoid,  $AUC_{0-\infty}$ , and percent excreted in urine over 1008 hrs. A comparison of the reviewer's values and the sponsor's values is shown in Table 3. The elimination half-life was calculated using the last five plasma concentrations (144, 312, 480, 648, and 984 hrs) after visual inspection of the log-linear relationship. The percent urinary excretion of dalbavancin

and OH-dalbavancin were calculated by integrating the average urinary excretion rate (mg per hr) at the midpoint time of the urine collection interval over the entire urine collection period (1008 hrs).

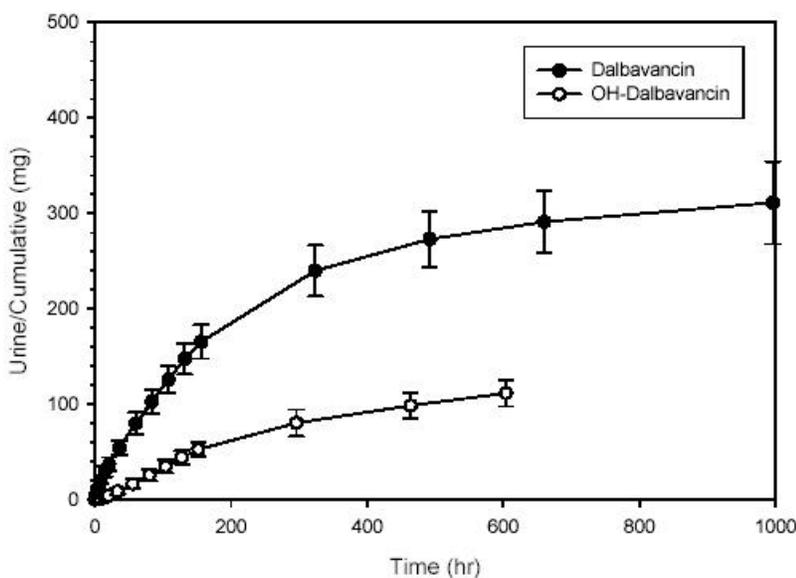
**Table 3. Comparison of mean (CV%) pharmacokinetic parameters calculated by the sponsor and reviewer**

Parameter	Sponsor	Reviewer
<b>Dalbavancin</b>		
AUC ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	24,453 (15%)	---
AUC <sub>0-984</sub> ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	---	24,144 (15%)
AUC <sub>0-∞</sub> ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	---	25,342 (16%)
Terminal trapezoid	---	1198 (29%)
t <sub>1/2</sub> (hrs)	261 (14%)	237 (7%)
Urinary excretion (mg)	330	312.6
<b>OH-Dalbavancin</b>		
Urinary excretion (mg)	117	111.6

The terminal trapezoid represented 4.7% of the mean total AUC when plasma samples were obtained for 984 hrs; thus, the mean AUC<sub>0-984</sub> and AUC<sub>0-∞</sub> values are similar. The sponsor's AUC value of 24,453 was within the AUC<sub>0-984</sub> and AUC<sub>0-∞</sub> values calculated by the reviewer. The mean elimination half-life calculated by the reviewer was less than the sponsor's value (237 hrs vs. 261). However, the mean percent of dalbavancin excreted in urine over 1008 hrs calculated by the reviewer was similar to the value reported by the sponsor (313 mg vs. 330 mg, respectively). Thus, the fraction of dalbavancin recovered unchanged in urine was approximately one-third of the administered dose (Figure 2).

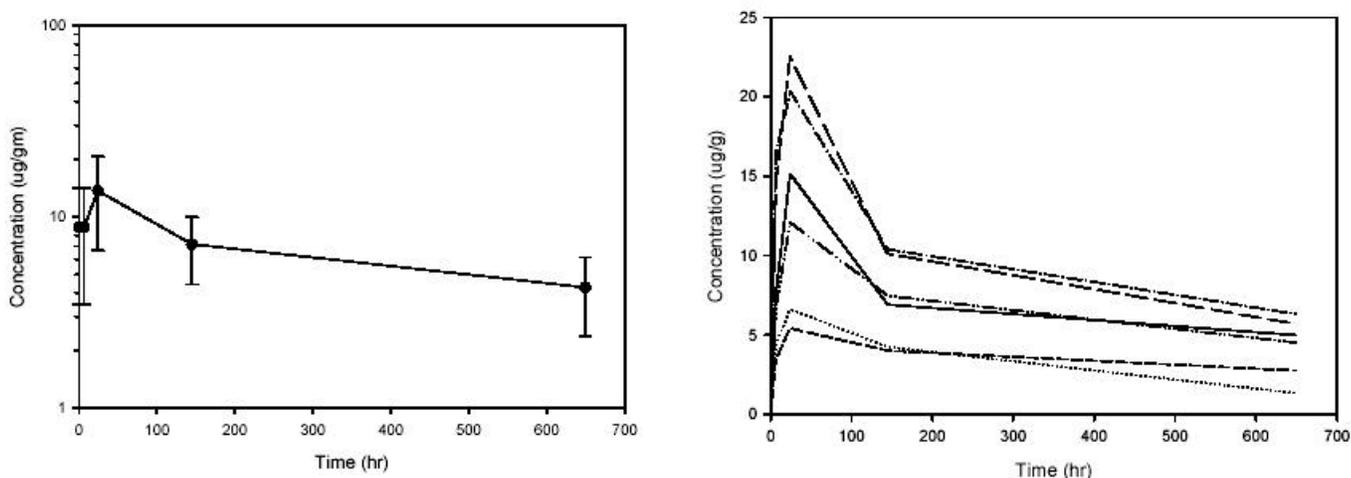
The concentrations of the primary metabolite of dalbavancin (OH-dalbavancin) in plasma were below quantifiable limits ( $<0.5 \mu\text{g}/\text{mL}$ ) in all subjects at all time points. However, OH-dalbavancin concentrations were quantifiable in urine. The cumulative amount of OH-dalbavancin excreted in urine averaged 117 mg (approximately 12% of the total dose). The mean percent of OH-dalbavancin excreted in urine over 1008 hrs calculated by the reviewer was 111.6 mg and is similar to the sponsor's value. The estimated amount of OH-dalbavancin excreted in the urine was 26% of the total amount of drug excreted in the urine.

**Figure 2. Mean cumulative amount of dalbavancin and OH-dalbavancin excreted in urine vs. time following administration of a single dose of dalbavancin 1000 mg**



The mean and individual concentration-time profiles of dalbavancin in skin are shown in Figure 3. The mean concentration of dalbavancin in skin peaked on day 2 (13.69  $\mu\text{g}/\text{mL}$ ) and declined to 7.19  $\mu\text{g}/\text{mL}$  and 4.27  $\mu\text{g}/\text{mL}$  on days 7 and 28, respectively. Individual dalbavancin skin concentrations on day 7 ranged from 4.01 to 10.39  $\mu\text{g}/\text{mL}$ .

**Figure 3. Mean (left) and individual (right) dalbavancin skin concentration-time profiles following administration of a single dose of dalbavancin 1000 mg**



The sponsor stated that the mean penetration of dalbavancin into skin was 36% by comparing the AUC from skin with the AUC from plasma. However, the reviewer determined that the mean penetration of dalbavancin into skin was only 20% (range 12% to 31%) using the  $\text{AUC}_{0-648}$  from skin and plasma. It appears that the sponsor used the skin AUC from  $\sim 28$  days ( $\text{AUC}_{0-672}$ ) and the plasma AUC from  $\sim 7$  days ( $\text{AUC}_{0-144}$ ).

The proposed susceptibility breakpoints of dalbavancin for *Staphylococcus aureus* and *Streptococcus* spp. are (b) (4) respectively. The protein binding of dalbavancin in plasma is approximately 93%. Although the protein binding of dalbavancin in interstitial fluid is likely to be lower than plasma, the mean peak unbound concentration of dalbavancin assuming a protein binding of 93% will not exceed a MIC of 1  $\mu\text{g}/\text{mL}$  (mean 0.96  $\mu\text{g}/\text{mL}$ , range 0.38 to 1.58  $\mu\text{g}/\text{mL}$ ).

#### **SAFETY:**

There were no deaths, life-threatening adverse events (AEs), serious AEs (SAEs) or premature discontinuations from study, or from study drug treatment due to AEs. All six subjects reported at least one AE, all of which were mild in intensity. Three subjects reported AEs that were considered possibly related to study drug.

Two subjects experienced an increased ALT (Subject 216 and 204). Subject 216 an elevated LDH, ALT, and AST within  $2 \times \text{ULN}$  on day 7; both ALT and AST returned to within the normal range by day 28. Subject 204 experienced an elevated ALT within  $2 \times \text{ULN}$  on day 7 and decreased to within the normal range by day 28.

All six subjects had ECGs performed at screening, day 1 (within 30 min after completion of dalbavancin infusion), and day 42. There were no clinically significant abnormal ECG results reported at any time point for any of the six subjects. At Screening, for the six subjects the mean QTcB was 390 msec, which

increased by only 1 msec to 391 msec on both Day 1 and Day 42. On Day 1 (within 30 minutes after completion of dalbavancin infusion), no subject had QTcB >60 msec, nor individual QTcB values >500 msec (on therapy at  $C_{max}$ ). Similar findings were observed on Day 42. The QT interval was not corrected using the formula of Fridericia.

**CONCLUSIONS:**

1. Excretion of unchanged dalbavancin in urine accounted for approximately one-third of the administered dose and excretion of OH-dalbavancin in urine accounted for an additional 12% of the administered dose.
2. Dalbavancin was capable of penetrating into skin, with a relative exposure of 36%. However, the protein binding of dalbavancin in interstitial fluid is unknown and dalbavancin may not be capable of exceeding the MIC of potential pathogens depending upon the actual protein binding at the site of the infection.

**COMMENTS:**

1. It is unclear from the study report which dalbavancin components (e.g.  $B_0$ ,  $B_1$ ,  $B_2$ ) the LC/MS/MS analytical method is detecting. The sponsor only states that a LC/MS/MS method was used for the determination of dalbavancin and its hydroxy metabolites in human plasma. The sponsor should clarify which components of dalbavancin are contributing to the reported dalbavancin and OH-dalbavancin concentrations.
2. The sponsor did not state whether skin biopsy samples were processed (homogenized) prior to determining dalbavancin concentrations, which can alter the drug concentration measured since dalbavancin is primarily contained in the extracellular water compartment. Without additional information, it is possible that the concentration of dalbavancin may be greater than those presented in the study report.

#### 4.2.12 A Phase I, open-label study to evaluate the safety, tolerability, and pharmacokinetics of intravenous Dalbavancin in subjects with severe renal impairment or end stage renal disease and healthy subjects with normal renal function (VER001-11)

##### Sponsor

Vicuron Pharmaceuticals  
455, South Gulph Road, Suit 310  
King of Prussia, PA 19406.

##### Objectives

##### Primary

- The primary objective of the study was to assess the pharmacokinetics of dalbavancin administered intravenously in subjects with severe renal impairment or end stage renal disease (ESRD) compared to age-, gender-, and weight-matched healthy subjects with normal renal function.

##### Secondary

- To recommend (if necessary) a dosage adjustment for subjects with severe renal impairment or ESRD.
- To examine the metabolite profile of dalbavancin by examining the plasma samples in all groups, the urine samples in severe renal impairment and normal renal function groups, and fecal samples from subjects in the normal renal function group.
- To explore the effect, if any, of dalbavancin in eradicating nasal colonization with *Staphylococcus aureus*.

##### Methodology

This was a Phase I, open label, single-dose study of dalbavancin administered by intravenous (IV) infusion over 30 minutes to otherwise healthy subjects with severe renal impairment or ESRD and to subjects with normal renal function. Twenty two subjects = 18 to 80 years of age with varying degrees of renal function based on creatinine clearance ( $CL_{cr}$ ) were enrolled in the study; 10 subjects in Group A, 6 subjects in Group B, and 6 subjects in group C.

**Table 1: Treatment Groups in Study VER001-11**

Group	Otherwise healthy subjects with:	$CL_{cr}$ (mL/min)
A1, A2	Severe renal impairment	< 30
B1, B2	End-stage renal impairment	dialysis-dependent
C	Normal renal function	= 80

Subjects in Group A were classified as having severe renal impairment according to the Cockcroft-Gault formula (< 30 mL/min) or on the basis of a 24-hour urine collection. Per the original protocol (June 20, 2003), 6 subjects in Group A were administered 500 mg dalbavancin (Group A1). Following a protocol amendment (25 February, 2004), 4 subjects were administered 1000 mg dalbavancin (Group A2). 6 subjects in Group B were classified as having end-stage renal impairment and were dependant on chronic dialysis. 3 subjects were administered dalbavancin (500 mg) prior to dialysis (Group B1), and 3 subjects were

administered dalbavancin after the completion of dialysis (Group B2). Control subjects with normal renal function (Group C) had an estimated  $CL_{cr} = 80$  mL/min. 6 control subjects were age-( $\pm 10$  years), weight (7 kg), and gender-matched to subjects in group A and B.

All subjects in Groups A1, B1, B2, and C received a single 500 mg IV dose of dalbavancin infused over 30 minutes on Day 1. Subjects in Group B1 received a single dose of dalbavancin infused prior to dialysis session and subjects in Group B2 received a single dose of dalbavancin infused after the dialysis session. All subjects in Group A2 received a single 1000 mg dose of dalbavancin administered intravenously over 30 minutes on Day 1.

Subjects with severe renal impairment (Group A1) receiving the 500 mg dose of dalbavancin were treated first. After safety and dalbavancin plasma concentration data through Day 14 were available for at least three subjects with severe renal impairment at the 500 mg dose, the data was reviewed by the sponsor to decide if the ESRD group (Group B) should receive the same or a modified dosage (subjects with severe renal impairment receiving the 1000 mg dose of dalbavancin were treated in parallel to the ESRD group).

The total duration of the study was approximately 6 months, with each enrolled subject's individual participation comprising 60 days.

### **Inclusion/Exclusion Criteria**

#### **Inclusion Criteria:**

- Male or female = 18 years of age and < 80 years of age;
- Estimated  $CL_{cr}$  of <30 mL/min according to the Cockcroft-Gault formula, non dialysis (severe renal impairment group), or dialysis-dependent (ESRD group), or = 80 mL/min (normal renal function group).

#### **Exclusion Criteria:**

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times upper limit of normal.
- Had a transplanted kidney, heart, or liver.
- Use of drugs of abuse and /or positive findings for drugs of abuse on urinary drug screening.
- Exposure to aminoglycoside antibiotics or chemotherapy with carboplatin, cisplatin, vincristine, or difluoromethylornithine in the last 6 months.
- Female subjects who are pregnant, lactating (breast feeding) or planning a pregnancy during the course of the study, including the screening period, or who were of child bearing potential and not using an acceptable method of birth control.

### **Investigational Product(s)**

Dalbavancin was provided as a preservative-free, sterile, lyophilized, white to off-white powder in 20 mL single-use vials. Each 200 mg vial contained 200 mg of dalbavancin, (b) (4) mannitol, and hydrochloric acid and/or sodium hydroxide for pH control.

## Drug Concentration Measurements

### Blood Collection

A total of 11 blood samples (10 mL each) were drawn for the assessment of study drug and possible metabolites in plasma at the following times: pre-infusion (blank sample), end of infusion (0.5 hours), and 4 and 12 hours post-start of infusion. In addition, blood samples were drawn on Days 2, 3, 7, 14, 28, 42, and 60.

For ESRD subjects in Group B1, dialysis treatment start and stop times were recorded and blood samples for pharmacokinetic analysis followed the scheduled times as closely as possible. The scheduled 4-hour blood sample followed the end of dialysis treatment. For ESRD subjects in Group B2, dialysis treatment start and stop times were recorded and blood samples for pharmacokinetic analysis followed the scheduled times.

### Dialysate Collection

Two sets of dialysate samples were collected from subjects in Group B (ESRD). The first set of samples were collected on Day 1 and the second set of samples were collected during one additional dialysis treatment occurring between study days 14 and 28. A minimum requirement of 3 subjects with dialysate in Group B was acceptable for purposes of analyzing concentrations of dalbavancin.

### Urine Collection

24-hour urine samples were collected for subjects with normal renal function and severe renal impairment (Group A and C). For subjects in Group A, urine samples were collected on Days 7, 14, 28, 42, and 60. For subjects in Group C, 24-hour urine samples were collected on Days 7, 14, 28, and 42.

### Fecal Collection

A minimum requirement of 3 subjects in Group C with fecal samples was considered acceptable for purposes of assessing the metabolite and excretion profile of dalbavancin. On days 1 through 3, 24-hour fecal collections began immediately post-start of infusion. Additional fecal collections were performed on Days 7, 14, 28, and 42 ( $\pm 1$  week). One final fecal sample was collected within one week of Day 60.

## Bioanalytical Measurements

Plasma samples were assayed for dalbavancin and dalbavancin metabolite (OH-dalbavancin) using a validated liquid chromatography coupled to tandem-mass spectrometry (LC-MS/MS) method [REDACTED] <sup>(b) (4)</sup>. The LC-MS/MS method for dalbavancin and OH-dalbavancin was validated in the concentration linear range of 1-128  $\mu\text{g/mL}$  for dalbavancin and 0.4-12.8  $\mu\text{g/mL}$  for OH-dalbavancin. It was further extended to 240  $\mu\text{g/mL}$  with a 10-fold dilution.

Overall precision for the quality control samples, as measured by percent relative standard deviation (% RSD) was = 10.8 % for dalbavancin and = 13.9 % for OH-dalbavancin. Overall accuracy, as measured by absolute percent relative error (% RE), for these quality control samples ranged from 1-10.3 % for dalbavancin and 2-7 % for OH-dalbavancin. Overall

precision and accuracy for the dilution integrity quality control samples was 2.82 % and 5 % respectively.

Human dialysate samples were analyzed for dalbavancin and OH-metabolite using LC-MS/MS method. A one-day partial validation using quality control samples prepared in the dialysate and calibration standards in human plasma was performed prior to sample analysis. The assay was validated over the nominal concentration range of 1-128 µg/mL for dalbavancin and 0.4-12.8 µg/mL for OH-dalbavancin.

## Pharmacokinetic Parameter Estimation

### Plasma

Dalbavancin and OH-Dalbavancin plasma and urine pharmacokinetic parameters were estimated using noncompartmental techniques. All measurements below the limit of quantitation (BQL) and no results (NR) values occurring at the end of the data set were treated as missing and appear in the data set as ".". All BQL and NR values occurring at the beginning of the data set prior to time to maximum plasma concentration ( $T_{max}$ ) were replaced by "0" instead of being treated as missing.

$C_{max}$  and  $T_{max}$  were obtained directly from the observed data.  $AUC_{0-t}$  (where t is day 7, Day 14, or last {time of last concentration}) was calculated using the log-linear rule. The area under the plasma concentration-time curve extrapolated to infinity (AUC or  $AUC_{0-inf}$ ) was calculated as the sum of  $AUC_{0-last}$  and  $C_{last}/terminal\ elimination\ rate\ constant\ (?_z)$ . The elimination half life ( $t_{1/2}$ ) was estimated by linear regression of the log-linear portion of the log concentration versus time curve. CL was computed as  $dose/AUC_{0-inf}$ . The volume of distribution at steady state ( $V_{ss}$ ) was calculated from the area under the first moment curve (AUMC) multiplied by the dose and divided by the AUC squared.

### Urine

The area under the urinary excretion rate curve (AURC) was calculated using the linear trapezoidal rule. The cumulative amount of dalbavancin excreted in urine was estimated as the AURC. The renal clearance ( $CL_r$ ) was calculated as the ratio:  $CL_{cr} = AURC_{0-last}/AUC_{0-last}$ . The non-renal clearance,  $CL_{nr}$ , was calculated as the difference between CL and  $CL_r$ .

## STUDY SUBJECTS

### Disposition

Table 1 shows the disposition of subjects in each treatment group that enrolled, discontinued and completed the study by treatment group.

**Table 1: Number of Subjects Enrolled, Discontinued, and Completed**

Status	Renal Function (Study Group)							Total
	Severe Impairment			End-Stage Renal Disease			Normal	
	A1	A2	A Total	B1	B2	B Total	C	
Enrolled	6	4 <sup>a</sup>	10	3	3	6	6	22 <sup>a</sup>
Discontinued	0	0	0	0	0	0	0	0
Completed	100%	100%	100%	100%	100%	100%	100%	100%

a: Three of these subjects were enrolled in both Group A1 and A2. A total of 19 unique subjects were evaluated in this study.

Group A1 = Severe renal impairment, 500 mg dalbavancin; Group A2 = Severe renal impairment, 1000 mg dalbavancin; Group B1 = End-stage renal disease, dialysis-dependent, 500 mg dalbavancin prior to dialysis; Group B2 = End-stage renal disease, dialysis-dependent, 1000 mg dalbavancin after dialysis; Group C = normal renal function.

As the footnote of the table indicates, three subjects (11001004, 11001002, and 11001005) met all entrance criteria at the second enrollment and were re-enrolled in Group A2.

### Withdrawals

There were no withdrawals from the study.

### Protocol Deviations

There were no protocol deviations leading to exclusion from the analyses.

### *Reviewers Note:*

*Although waivers were provided to certain subjects in all the dosing groups for not meeting the entry requirements (higher body weight, presence of cardiovascular abnormalities etc), none of the subjects were excluded from the pharmacokinetic and statistical analysis.*

### **Demographics and Other Baseline Characteristics**

Table 2 shows the demographic and baseline characteristics for the study population.

Characteristic	Renal Function				
	Severe Renal Impairment		End-Stage Renal Disease		Normal
	Group A1	Group A2	Group B1	Group B2	Group C
Age (yrs) (mean ± sd)	54.3 ± 13.4	65.8 ± 6.3	55.3 ± 15.0	55.3 ± 4.9	50.5 ± 12.6
Height (cm) (mean ± sd)	169.2 ± 5.0	170.3 ± 4.7	166.8 ± 9.8	176.0 ± 3.6	171.2 ± 11.1
Weight (kg) (mean ± sd)	79.5 ± 20.6	83.6 ± 19.7	66.9 ± 16.8	89.2 ± 21.4	87.3 ± 21.0
Study CL <sub>cr</sub> <sup>a</sup> (mL/min) (mean ± sd)	18.7 ± 6.1	19.9 ± 7.6	na	na	100.5 ± 12.3

CL <sub>cr</sub> on Day 1-2 <sup>b</sup> (mL/min) (mean ± sd)	17.2 ± 6.0	20.8 ± 8.4	na	na	90.2 ± 26.6
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a: Study CL<sub>cr</sub> was determined using the Cockcroft-Gault formula for serum creatinine levels and IBW or by a 24-hour urine collection. This is the measurement that was used for entrance criteria to the study and in all pharmacokinetic analysis.

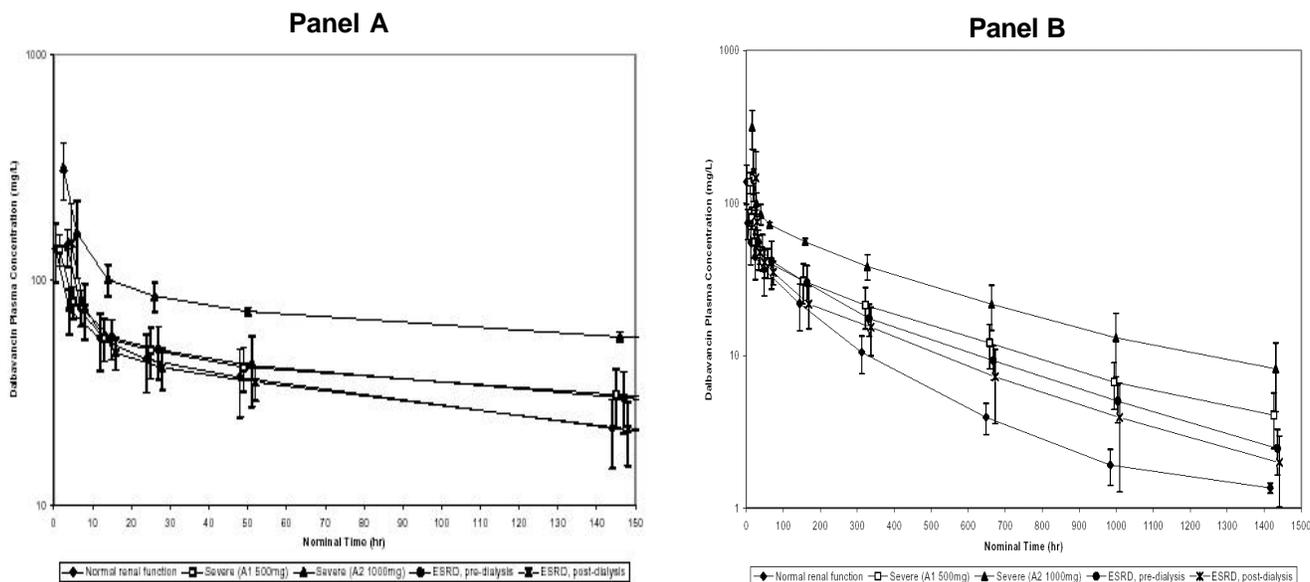
b: CL<sub>cr</sub> was determined using a 24-hour urine collection.

### Pharmacokinetic Results

#### Plasma

Fig 1 shows the mean (± sd) dalbavancin plasma concentration-time profile following administration of 500 mg or 1000 mg dalbavancin in subjects with normal renal function, severe renal impairment, or ESRD. The profiles are presented on two time scales: 0-150 hours (panel A) and 0-1500 hours (panel B).

**Fig 1: Mean (± SD) Dalbavancin Plasma Concentration-Time Profiles Following Administration of 500 mg or 1000 mg Dalbavancin in Subjects with Normal Renal Function, Severe Renal Impairment, or ESRD. The profiles are presented on two time scales: 0-150 hours (panel A) and 0-1500 hours (panel B)**



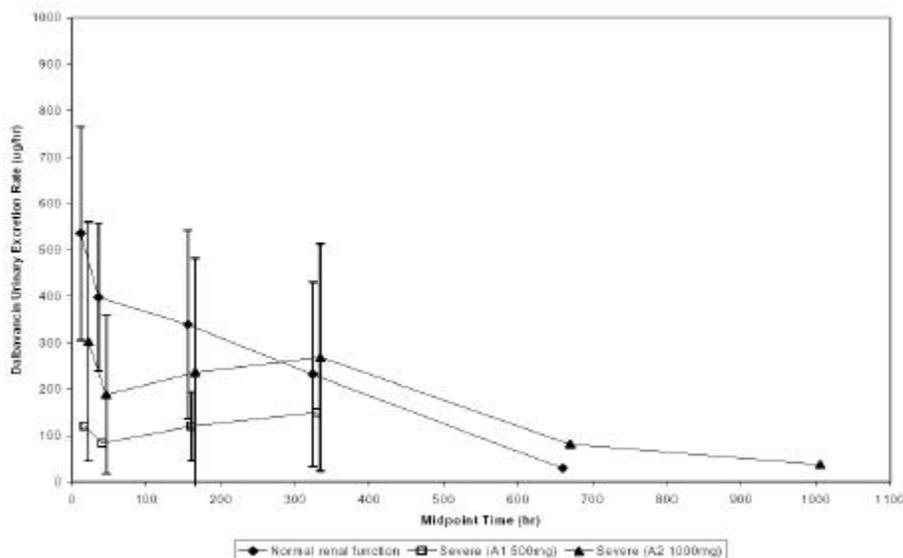
#### Dalbavancin Dialysate and Dialyzed Blood

Arterial and venous blood samples were drawn from the dialyzer for subjects in group B and analyzed for dalbavancin. There was no apparent decrease in concentrations from the venous port compared to the arterial port. Dialysate samples were also taken for each of the subjects and assayed for dalbavancin. All measurements were below LLQ.

## Dalbavancin in Urine

Fig 3 shows the mean urinary excretion rate-time profiles for dalbavancin.

**Fig 3: Mean ( $\pm$  SD) Dalbavancin Urinary Excretion Rate-Time Profiles Following Administration of 500 and 1000 mg Dalbavancin in Subjects with Normal Renal Function and Severe Renal Impairment**



## Dalbavancin in Feces

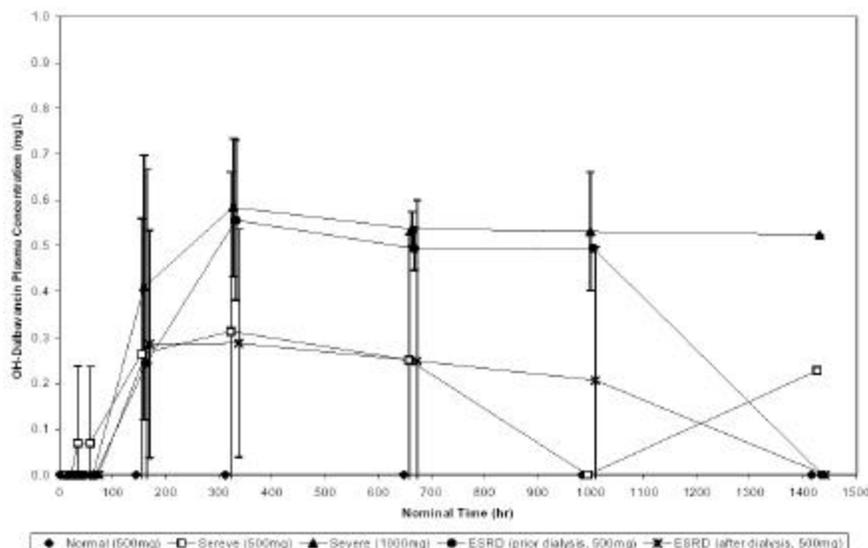
As most of the measurements were below LLOQ, summary statistics for the amount of dalbavancin excreted in the feces and mean fecal excretion rate-time profiles could not be calculated.

## OH-Dalbavancin

### Plasma

Fig 4 shows the mean profiles of OH-dalbavancin plasma concentration-time data by study group. The summary statistics for OH-dalbavancin plasma concentration data by study group were not available because an insufficient number of OH-dalbavancin plasma concentration values were above the LLOQ (0.4 mg/L).

**Fig 4: Mean ( $\pm$  SD) OH-Dalbavancin Plasma Concentration-Time Profiles Following Administration of 500 mg or 1000 mg Dalbavancin in Subjects with Normal Renal Function, Severe Renal Impairment, or ESRD.**



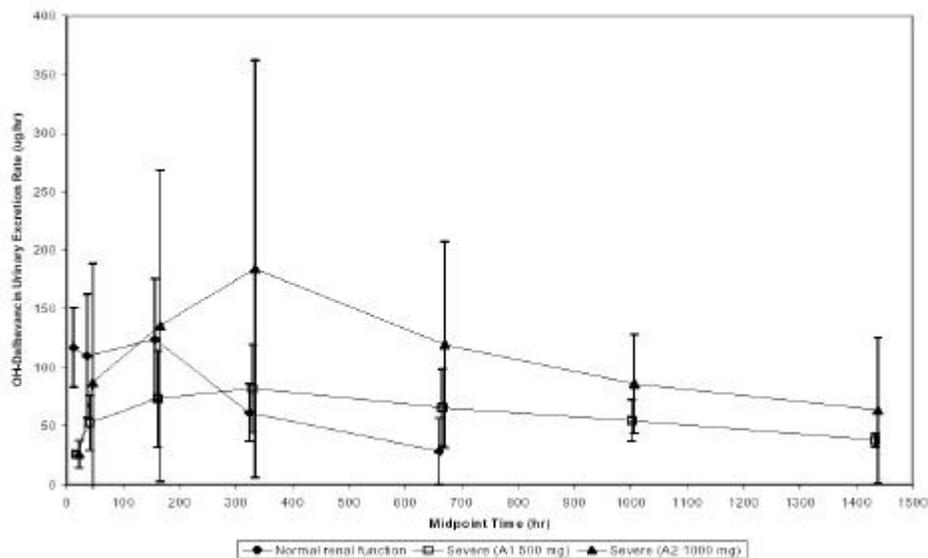
Dialysate and Dialyzed Blood

Arterial and venous blood samples were drawn from the dialyzer for subjects in Group B (ESRD) and plasma was evaluated for OH-Dalbavancin. There were no measurable OH-dalbavancin concentrations from either the venous or arterial port.

Urine

Fig 5 shows the mean urinary excretion rate-time profiles for OH-dalbavancin. The amount of OH-dalbavancin excreted in the urine was low and comparable between subjects with normal renal function and subjects with severe renal impairment.

**Fig 5: Mean ( $\pm$  SD)OH-Dalbavancin Urinary Excretion Rate-Time Profiles Following Administration of 500 and 1000 mg Dalbavancin in Subjects with Normal Renal Function or Severe Renal Impairment**



## PHARMACOKINETIC DATA ANALYSIS RESULTS

### Dalbavancin

#### Plasma

Table 3 shows the summary of the PK parameters. Subjects with severe renal impairment receiving 500 mg dalbavancin had a 100 % increase in  $AUC_{0-inf}$  compared to subjects with normal renal function. However, comparison of  $AUC_{0-day 7}$  and  $AUC_{0-day14}$  between study groups showed only a respective 16 % and 31 % increase in exposure in subjects with severe renal impairment compared to subjects with normal renal function.  $C_{max}$  was similar across all treatment groups.

#### Reviewer's Comment:

*As dalbavancin is a long half drug, the change of drug concentrations is not significant in a given time interval. This may partly explain the similarity of  $AUC_{0-day 7}$  and  $AUC_{0-day14}$  between the three treatment groups.*

Compared to subjects with normal renal function, subjects with ESRD had an increase in  $AUC_{0-inf}$ . The increase in  $AUC_{0-inf}$  was 62 % and 28 % respectively for subjects in study groups B1 and B2 compared to subjects with normal renal function. The mean  $AUC_{0-day 7}$  and  $AUC_{0-day14}$  for subjects with ESRD was comparable to that for subjects with normal renal function, with a mean increase of only 5 % and 20 % respectively.  $C_{max}$  was not increased in subjects with ESRD (Groups B1 and B2) when compared to subjects with normal renal function. (Group C).

**Table 3: Mean ( $\pm$  SD) Dalbavancin Plasma Pharmacokinetic Parameters**

	Severe Renal Impairment <sup>a</sup> (500 mg) Group A1 (N = 6)	Severe Renal Impairment <sup>a</sup> (1000 mg) Group A2 (N = 4)	End Stage Renal Disease (pre-dialysis) (500 mg) Group B1 (N = 3)	End Stage Renal Disease (post-dialysis) (500 mg) Group B2 (N = 3)	Normal Renal Function <sup>b</sup> (500 mg) Group C (N = 6)
$C_{max}$ (mg/L)	136.5 (21.6)	315.3 (89.7)	140.7 (26.4)	145.8 (71.5)	137.3 (39.5)
% CV	15.83	28.46	18.76	49.05	28.78
$T_{max}$ (hr) <sup>c</sup>	0.54	0.55	0.55	0.58	0.51
Range	(0.50 – 0.65)	(0.50 – 0.60)	(0.50 – 0.62)	(0.50 – 0.65)	(0.50 – 0.52)
$AUC_{0-inf}$ (hr <sup>2</sup> mg/L)	6077 (1392)	10653 (1474)	6069 (1768)	4969 (1153)	5245 (1661)
% CV	22.91	13.84	29.13	23.20	31.68
$AUC_{0-day14}$ (hr <sup>2</sup> mg/L)	10412 (2658)	18698 (1780)	10620 (2881)	8500 (2297)	7971 (2422)
% CV	25.53	9.52	27.13	27.02	30.39
$AUC_{0-48}$ (hr <sup>2</sup> mg/L)	24074 (6613)	44497 (11483)	19772 (5065)	15587 (6050)	12219 (3298)
% CV	27.47	25.81	25.62	38.81	26.99
$V_{ss}$ (L)	13.2 (2.9)	14.2 (0.8)	12.8 (3.4)	14.6 (3.2)	15.0 (4.2)
% CV	21.70	5.62	26.39	22.00	28.22
CL (L/hr)	0.0222 (0.0064)	0.0238 (0.0068)	0.0264 (0.0063)	0.0350 (0.0113)	0.0429 (0.0092)
% CV	28.88	28.73	23.98	32.24	21.37
$t_{1/2}$ (hr)	454 (102)	469 (103)	376 (63)	347 (78)	333 (91)
% CV	22.52	21.96	16.83	22.37	27.36

a: Severe renal impairment ( $CL_{cr} < 30$  mL/min)

b: Normal renal function ( $CL_{cr} > 80$  mL/min)

c: Values for  $T_{max}$  represent Median (Range)

Abbreviations: CV=coefficient of variation, SD=standard deviation, AUC=area under the plasma concentration-time curve,

$C_{max}$ =maximum observed plasma concentration,  $T_{max}$ =time of maximum observed plasma concentration,  $t_{1/2}$ =terminal elimination half-life, CL=clearance,  $V_{ss}$ =volume of distribution at steady state

Reviewer's Comment:

The sponsor has provided scatter plots of dose normalized  $C_{max}$ ,  $AUC_{0-day 7}$ ,  $AUC_{0-day 14}$ , and  $AUC_{0-infinity}$  as a function of the modified screening creatinine clearance. It is not clear why the sponsor dose-normalized the PK parameters (since the doses administered to the three groups are the same). Further, since the sponsor has indicated that there are no significant differences in AUC's ( $AUC_{0-day 7}$ ,  $AUC_{0-day 14}$ ) between the three treatment groups, the only significant relationship that can be expected in terms of exposures (as determined by AUC) and the degree of renal impairment is in the scatter plot of  $AUC_{0-inf}$  as a function of modified creatinine clearance; subjects with lower creatinine clearance are expected to have higher  $AUC_{inf}$  due to the higher degree of extrapolation.

Urine

Table 4 shows the summary statistics of dalbavancin urine pharmacokinetic parameters by study group. Information is presented for only two subjects in the severe renal impairment group receiving 500 mg dalbavancin (A1) because most subjects had dalbavancin concentration values in the urine below the LLQ at all time points. Due to the long half life and limitations of the urine sampling scheme, the total amount of dalbavancin ( $A_e$ ) excreted in the urine could not be estimated directly by sampling.  $AURC_{0-last}$  was used as an estimate of the total amount of dalbavancin excreted in the urine and  $CL_r$  was calculated as  $AURC_{last}/AUC_{0-last}$ . The estimated fraction of dalbavancin excreted in the urine was 4.87 % for group 1 (severe renal impairment receiving 500 mg dalbavancin), 7.63 % for group A2 (severe renal impairment receiving 1000 mg dalbavancin) and 14.94 % for group C (normal renal function) of the total dose administered, based on the  $AURC_{0-last}$  calculation.

**Table 4: Mean ( $\pm$  SD) Dalbavancin Urine Pharmacokinetic Parameters**

	Severe Renal Impairment <sup>a,c</sup> (500 mg) Group A1 (N = 2)	Severe Renal Impairment <sup>a</sup> (1000 mg) Group A2 (N = 4)	Normal Renal Function <sup>b</sup> (500 mg) Group C (N = 6)
<b>AURC<sub>0-last</sub> (mg)</b>	24.3	76.3 (66.0)	74.7 (57.0)
<b>% CV</b>	(10.4 – 38.3)	86.50	76.26
<b>CL<sub>r</sub> (L/hr)</b>	0.00162	0.00226 (0.00245)	0.00621 (0.00412)
<b>% CV</b>	(0.00054 – 0.00270)	108.33	66.33
<b>CL<sub>nr</sub> (L/hr)</b>	0.0268	0.0215 (0.0049)	0.0367 (0.0110)
<b>% CV</b>	(0.0234 – 0.301)	22.92	29.98

a: Severe renal impairment ( $CL_{cr} < 30$  mL/min)

b: Normal renal function ( $CL_{cr} > 80$  mL/min)

c: N=2, therefore parameters presented as median (range)

Abbreviations: CV=coefficient of variation, AURC=area under the urine excretion rate curve,  $CL_r$ =renal clearance,  $CL_{nr}$ =non-renal clearance

**OH-Dalbavancin**Plasma

All quantifiable OH-dalbavancin plasma concentrations were low and only just above the LLQ for the assay (LLQ = 0.4 µg/mL).

Urine

Table 5 shows the summary statistics of the dalbavancin metabolite urine pharmacokinetic parameters by study group.

**Table 5: Mean (± SD) OH-Dalbavancin Urine Pharmacokinetic Parameters**

	Severe Renal Impairment <sup>a</sup> (500 mg) Group A1 (N = 6)	Severe Renal Impairment <sup>a</sup> (1000 mg) Group A2 (N = 4)	Normal Renal Function <sup>b</sup> (500 mg) Group C (N = 6)
AUC <sub>0-last</sub> (hr*mg/hr)	66.1 (35.0)	129.9 (68.4)	34.7 (20.2)
% CV	52.88	52.66	58.33

a: Severe renal impairment (CL<sub>cr</sub> < 30 mL/min)

b: Normal renal function (CL<sub>cr</sub> > 80 mL/min)

**DOSING RECOMMENDATIONS**

The overall exposure to dalbavancin, as assessed by AUC<sub>0-inf</sub> was higher for subjects with severe renal impairment compared to those with normal renal function. Subjects with ESRD had an overall exposure that was increased, although to a lesser extent, but had similar concentrations and drug exposures compared to subjects with normal renal function through the 14-day treatment interval.

Reviewer's Comment regarding Dose Adjustment

(b) (4)

*In the opinion of this reviewer, from an exposure-efficacy point of view, there is no need of dose adjustment (due to similarity in exposures between the three treatment groups during the 14 day treatment period). However, dose may need to be adjusted in subjects with severe renal impairment from a safety point of view.*

Mean dalbavancin concentrations from groups A1 (severe renal impairment) and C (normal renal function) were fitted to a two-compartment pharmacokinetic model (Winnonlin Version 4.1; Pharsight Corporation, Mountain View CA). Table 6 shows the pharmacokinetics obtained from modeling. The models reflected an approximately 50 % decrease in total CL for subjects with severe renal impairment.

**Table 6: Two-compartment pharmacokinetic model fit using dalbavancin plasma concentrations from subjects with normal renal function and subjects with severe renal impairment.**

Parameter <sup>b</sup>	Normal Renal Function		Severe Renal Impairment <sup>a</sup>	
	Estimate	CV%	Estimate	CV%
V1	3.44	2.5	3.51	2.5
CL	0.0540	10.9	0.0264	11.5
V2	5.53	7.8	6.14	7.1
CLD2	0.762	11.0	0.621	10.2

a: Mean dalbavancin concentrations through 648 hours (27 days) for each group (A1 and C) were fit to a two-compartment model using WinNonlin Professional Ver. 4.1 (Model 9; Gauss-Newton method)

b: Parameters: volume of distribution of the central compartment (V1); total clearance (CL); volume of distribution of the peripheral compartment (V2); inter-compartmental clearance (CLD2)

Simulations were then performed for examining various dosage-adjusted regimens for subjects with severe renal impairment. To determine an appropriate regimen, attempts were made to minimize the overall exposure of the drug, while maintaining concentrations above the same levels observed for subjects with normal renal function through the 14-day treatment interval ( $C_{336h} > 34.5$  mg/L). Further, exposures had to be similar to treatment period exposures ( $AUC_{336h}$ ) observed in subjects with normal renal function.

Table 7 shows the simulated exposure parameters for patients with severe renal impairment receiving different dose-adjustment regimens.

**Table 7: Simulated exposure parameters for patients with severe renal impairment receiving different doses-adjustment regimens. Parameters are compared to patients with normal renal function receiving 1000 mg dalbavancin (day 1) and 500 mg dalbavancin (day 8)<sup>a</sup>.**

Population/ Dosage (Day 1 + Day 8)	C <sub>max1</sub> (mg/L)	C <sub>max2</sub> (mg/L)	C <sub>336h</sub> (mg/L)	AUC <sub>168h</sub> (mg.h/L)	AUC <sub>336h</sub> (mg.h/L)	AUC <sub>inf</sub> (mg.h/L)
Normal Renal Function						
1000 + 500 mg	274	177	34.5	11776	21890	27789
Severe Renal Impairment						
1000 + 500 mg	272	200	72.4	14160	29851	56761
1000 + 250 mg	272	132	56.5	14160	26311	47301
1000 + 125 mg	272	98	48.5	14160	24541	42571
1000 mg	272	n/a	40.5	14160	22771	37841
750 + 250 mg <sup>b</sup>	204	116	46.3	10620	20618	37841
750 + 125 mg	204	82	38.3	10620	18848	33111
750 mg	204	n/a	30.4	10620	17078	28381
500 + 250 mg	136	100	36.2	7080	14925	28381
500 mg	136	n/a	20.3	7080	11385	18921

- a: Simulated using a two-compartment model fit with mean observations from VER001-11 (normal renal function and severe renal function) using WinNonlin. Parameters include the maximum concentrations following the first dose (C<sub>max1</sub>) and second dose (C<sub>max2</sub>), minimum concentrations maintained through the 2-week treatment period (C<sub>336h</sub>), and exposure through 1-week post-dose (AUC<sub>168h</sub>), 2-weeks post-dose (AUC<sub>336h</sub>), and extrapolated through infinity (AUC<sub>inf</sub>).

b:  (b) (4)

**Reviewer's Comment regarding Sponsor's Dose Selection for Subjects with Severe Renal Impairment**

(b) (4)

However, on the basis of predicted exposures provided by the sponsor (table 7) and the simulation performed by this reviewer, a 1000 mg single dose administered on day 1  (b) (4) meets both the criteria outlined above and may potentially result in better patient compliance.

(b) (4)



Fig 7 (constructed based on reviewer's analysis) shows the simulated concentration vs time profile of dalbavancin at the reviewer's proposed dosing regimen. The simulated concentration time profile in subjects with normal renal function and in subjects with severe renal impairment is provided for comparison purposes.

**Fig 7: Simulated Dalbavancin Concentration Time Profile at the Reviewer's Proposed Dosing Regimen (1000 mg single dose). The simulated concentration time profile in subjects with normal renal function and in subjects with severe renal impairment is provided for comparison purposes.**

(b) (4)

#### **Additional Modeling and Simulation Performed by the Reviewer**

The sponsor simulated various plasma concentrations versus time profiles to determine the optimum regimen of dalbavancin for subjects with severe renal impairment. The pharmacokinetic parameters used in the simulations were obtained after fitting a two compartmental model to the mean pharmacokinetic data obtained after administration of 500 mg dalbavancin as a 30 min infusion to subjects with severe renal impairment and subjects with normal renal function. An assumption was made that the pharmacokinetic parameters obtained in the severe renal impairment group are independent of the dose administered, hence PK parameters generated using the 500 mg dose can be used to simulate exposures at higher doses. However, this assumption may not be true because clearance mechanisms may get saturated at higher doses. This may lead to incorrect dosing recommendations for subjects with renal impairment.

The following steps were performed to verify the sponsor's analysis and to test the assumption of similarity of PK parameters across doses. All modeling and simulations were performed using Winonlin® (Version 4, Pharsight, CA).

- Mean concentration-time data obtained after administration of 500 mg dalbavancin was fitted to a two-compartment pharmacokinetic model. The pharmacokinetic parameters obtained were compared with the sponsor's estimates. Table 8 shows the comparison between the pharmacokinetic parameters obtained by the sponsor and the reviewer.

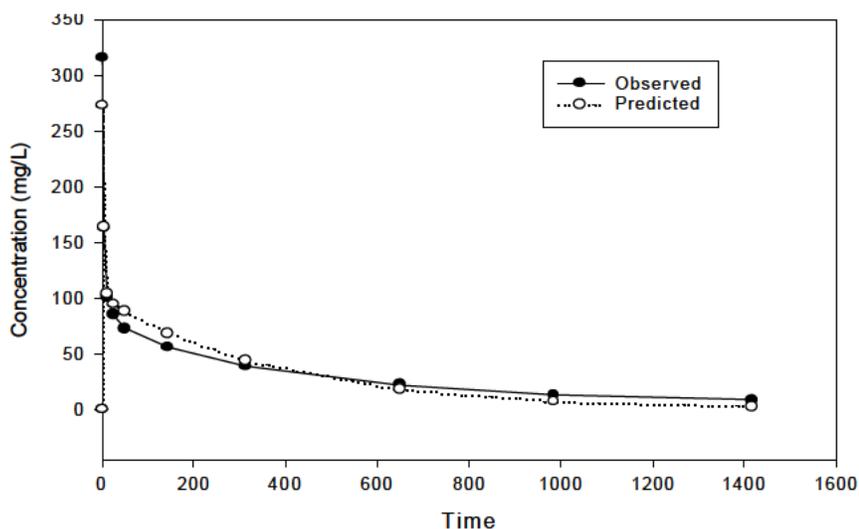
**Table 8: Comparison of pharmacokinetic parameters obtained (by the Sponsor and the Reviewer) from fitting a two compartment model to mean plasma concentration-time data obtained after administration of 500 mg dalbavancin to subjects with severe renal impairment.**

Parameter	Severe Renal Impairment			
	Sponsor's Analysis		Reviewer's Analysis	
	Estimate	CV (%)	Estimate	CV (%)
V1	3.51	2.5	3.51	2.42
CL	0.0264	11.5	0.0245	10.23
V2	6.14	7.1	6.31	6.63
CLD2 (Intercompartment Clearance)	0.621	10.2	0.61	9.78

The parameters obtained by this reviewer were nearly identical to the parameters obtained by the sponsor. This independently confirmed the appropriateness of the model.

- To test the assumption of similarity in PK parameters across doses in subjects with severe renal impairment, the parameters generated at the 500 mg dose were used to simulate the concentration time profile at the 1000 mg. The simulated concentration time profile was compared with the observed data obtained after administration of 1000 mg dalbavancin to subjects with severe renal impairment. Fig 8 shows the comparison.

**Fig 8: Comparison of Observed\* and Predicted\*\* Concentration as a function of time in subjects with severe renal impairment.**



\*: After administration of 1000 mg dalbavancin, as reported by sponsor; \*\*: (using a 1000 mg dose and PK parameters obtained from fitting the concentration-time data obtained after administration of 500 mg dalbavancin.

The results from the additional modeling and simulation confirmed the sponsor's model selection and support the use of pharmacokinetic parameters generated at 500 mg dose for the purposes of simulation at various dosing regimens. **On the basis of modeling and simulation**

performed by this reviewer and the comparison of exposure estimates provided by the sponsor at various dosing regimens, this reviewer proposes a single 1000 mg IV dose of dalbavancin in subjects with severe renal impairment (CL<sub>cr</sub> < 30 mL/min).

#### PHARMACOKINETIC CONCLUSIONS (As provided by the sponsor)

- Through 7 days post dose, dalbavancin plasma concentrations were similar among subjects with normal renal function and subjects with either severe renal impairment or ESRD. A small but consistent increase in concentrations beyond the first week, post-dose was observed in subjects with severe renal impairment.
- Dalbavancin and the hydroxyl metabolite were excreted in the urine. Compared to subjects with normal renal function, lower amounts of dalbavancin were excreted in subjects with severe renal impairment. Although the limitations of the urine-sampling scheme employed in the study did not allow for an accurate estimation of CL<sub>r</sub>, there was an apparent reduction in renal clearance in subjects with severe renal impairment and ESRD.
- No measurable concentrations of dalbavancin was found in the dialysate and there was no apparent reduction in dalbavancin concentration across arterial-venous sampling. Dalbavancin administration to subjects with ESRD resulted in similar concentration-time profiles during the first week regardless of whether dalbavancin was administered prior to or after the dialysis session.
- Fecal excretion of dalbavancin could not be measured in subjects receiving the 500 mg dose; concentrations were below the LLOQ for this dosage.

•  (b) (4)

*This reviewer recommends a single 1000 mg dose.*

#### 4.2.13 A Phase I, open-label study to evaluate the safety, tolerability, and pharmacokinetics of intravenous dalbavancin in subjects with mild, moderate, and severe hepatic impairment and healthy subjects with normal hepatic function (VER001-12)

##### Sponsor

Vicuron Pharmaceuticals  
455, South Gulph Road, Suit 310  
King of Prussia, PA 19406.

##### Objectives

###### Primary

- The primary objective of this Phase I study was to investigate the safety, tolerability, and pharmacokinetics of dalbavancin in subjects with mild, moderate and severe hepatic impairment compared to age-, gender-, and weight-matched healthy subjects with normal hepatic function.

###### Secondary

- If necessary, a secondary objective was to recommend a dosage adjustment for subjects with mild, moderate, or severe hepatic impairment.

##### Methodology

This was a Phase I, open label, multiple-dose study of intravenous (IV) dalbavancin administered (as a regimen of a 1000 mg IV dose infused over 30 minutes on Day 1 followed by a 500 mg IV dose infused over 30 minutes on Day 8) to subjects with mild, moderate, or severe hepatic impairment and to subjects with normal hepatic function. The Child-Pugh score was utilized to assess entry criteria and to assign subjects into the appropriate hepatic impairment study group. Up to 36 subjects = 18 to = 80 years with varying degrees of hepatic function were to be entered into the study. Table 1 shows the various groups and the associated Child-Pugh scores.

**Table 1: Treatment Groups and Associated Child-Pugh Scores**

Group	Otherwise healthy subjects with:	Child-Pugh Class
A	Mild Hepatic Impairment	Class A (5-6 points)
B	Moderate Hepatic Impairment	Class B (7-9 points)
C	Severe Hepatic Impairment	Class C (10-15 points)
D	Normal Hepatic Function	N/A

The groups were enrolled sequentially, beginning with subjects with Child-Pugh Class A (mild hepatic impairment), followed by subjects with Child-Pugh Class B (moderate hepatic impairment) and ending with subjects with Child-Pugh Class C (severe hepatic impairment). Control subjects with normal hepatic function were to be recruited throughout the study to match the enrolled hepatically impaired subjects with respect to age, weight, and gender.

## Inclusion/Exclusion Criteria

### Inclusion Criteria:

- Male or female = 18 years of age and < 80 years of age.
- Age ( $\pm$  10 years), weight ( $\pm$  7 kg), and gender-matched subjects enrolled into the normal hepatic function group must be healthy adults with healthy hepatic function and no clinically significant findings on clinical, laboratory or ECG evaluations.
- Able to abstain from alcohol from 48 hours before study drug infusion until the end of the in-house period.

### Exclusion Criteria:

- Creatinine clearance < 80 mL/min.
- Had a transplanted kidney, heart or liver.
- Use of any drug that might affect hepatic microsomal enzyme activity (e.g., barbiturates, phenytoin, cimetidine, rifampin, ketoconazole) within a three week period prior to screening.

## Investigational Product(s)

Dalbavancin was provided as a preservative-free, sterile, lyophilized, white powder in 20 mL single-use vials. Each vial contained 200 mg of dalbavancin, (b) (4) mannitol, and hydrochloric acid and/or sodium hydroxide for pH control.

## Drug Concentration Measurements

### Blood Collection

A total of 15 blood samples (10 mL each) were drawn at the following times: pre-infusion (blank sample), end of infusion (0.5 hours), and 4 and 12 hours post-start of infusion on Days 1 and 8. In addition, blood samples were drawn on Days 2, 4, 11, 15, 22, 29, and 60.

## Bioanalytical Measurements

Plasma samples were assayed for dalbavancin and dalbavancin metabolite (OH-dlbavancin) using a validated liquid chromatography coupled to tandem-mass spectrometry (LC-MS/MS) method (b) (4). The LC-MS/MS method for dalbavancin and OH-dalbavancin was validated in the concentration linear range of 1-128  $\mu\text{g/mL}$  for dalbavancin and 0.4-12.8  $\mu\text{g/mL}$  for OH-dalbavancin. It was further extended to 240  $\mu\text{g/mL}$  with a 10-fold dilution.

Overall precision for the quality control samples, as measured by percent relative standard deviation (% RSD) was = 8.48 % for dalbavancin and = 18.8 % for OH-dalbavancin. Overall accuracy, as measured by absolute percent relative error (% RE), for these quality control samples ranged from 1-10.5 % (absolute) for dalbavancin and 0-9.4 % (absolute) for OH-dalbavancin. Overall precision and accuracy for the dilution integrity quality control samples was 4.79 % for dalbavancin. Overall accuracy for the dilution integrity quality control samples was 0.83 % for dalbavancin.

## Pharmacokinetic Parameter Estimation

### Plasma

Dalbavancin and OH-Dalbavancin plasma and urine pharmacokinetic parameters were estimated using noncompartmental techniques (Winnonlin™ Professional Network Edition, Version 4.0.1, Pharsight Corp, Palo Alto, CA). All measurements below the limit of quantitation (BQL) and no results (NR) values occurring at the end of the data set were treated as missing and appear in the data set as ".". All BQL and NR values occurring at the beginning of the data set prior to time to maximum plasma concentration ( $T_{max1}$ ) were replaced by "0" instead of being treated as missing.

$C_{max1}$ ,  $C_{max2}$ ,  $T_{max1}$ , and  $T_{max2}$  were directly obtained from the observed data.  $AUC_{0-t}$  (where t is day 8, Day 15, or last {time of last concentration}) was calculated using the log-linear trapezoidal rule. The area under the plasma concentration-time curve extrapolated to infinity (AUC or  $AUC_{0-inf}$ ) was calculated as the sum of  $AUC_{0-last}$  and  $C_{last}/$ terminal elimination rate constant ( $\lambda_z$ ). The elimination half life ( $t_{1/2}$ ) was estimated by linear regression of the log-linear portion of the log concentration versus time curve. CL was computed as dose/ $AUC_{0-inf}$ . The volume of distribution at steady state ( $V_{ss}$ ) was calculated from the area under the first moment curve (AUMC) multiplied by the dose and divided by the AUC squared.

## STUDY SUBJECTS

### Disposition

The study enrolled 27 subjects in 4 groups: 6 subjects with mild hepatic impairment (Group A), 6 subjects with moderate hepatic impairment (Group B), 5 with severe hepatic impairment (Group C), and 10 with normal hepatic function (Group D).

One subject in the normal hepatic function group (12001020) withdrew from the study prematurely and was not included in the pharmacokinetics evaluable group. Table 1 shows the disposition of subjects in each treatment group that enrolled, discontinued and completed the study by treatment group.

**Table 1: Number of Subjects Enrolled, Discontinued, and Completed**

	<b>Hepatic Impairment Function (Study Group)</b>			
	Mild Impairment	Moderate Impairment	Severe Impairment	Normal Function
	(A)	(B)	(C)	(D)
Enrolled	6	6	5	10
Discontinued	0	0	0	1
Completed	6	6	5	9

Withdrawals

As previously indicated, subject 12001020 withdrew prematurely from the study due to personal reasons. The subject received study medication on Day 1 and withdrew consent prior to returning to the clinic for the second dose of study medication on Day 8. The subject returned to the clinic to have Day 60 assessments performed prior to withdrawal. The subject was not replaced.

*Reviewers Note:*

*Although enrollment exception were provided to certain subjects for not meeting inclusion criteria 9 (audiology assessment criteria), none of the subjects were excluded from the pharmacokinetic and statistical analysis. The subjects were granted an exception since the protocol was in the process of being amended to remove audiology as an inclusion criteria.*

**Demographics and Other Baseline Characteristics**

Table 2 shows the demographic and baseline characteristics for the study population.

**Table 2: Demographics and Baseline Characteristics**

<b>Characteristic</b>	<b>Hepatic Impairment, Study Group</b>			
	<b>Group A</b>	<b>Group B</b>	<b>Group C</b>	<b>Normal</b>
Age (yrs) (mean ± sd)	44.7 ± 8.5	53.2 ± 6.7	49.4 ± 7.2	50.8 ± 8.9
Height (cm) (mean ± sd)	168.4 ± 11.7	174.0 ± 5.6	170.9 ± 11.7	172.3 ± 11.9
Weight (kg) (mean ± sd)	89.8 ± 22.0	83.4 ± 9.6	93.7 ± 21.1	85.7 ± 18.2
Child-Pugh Score	5.7	8.3	10.6	NA

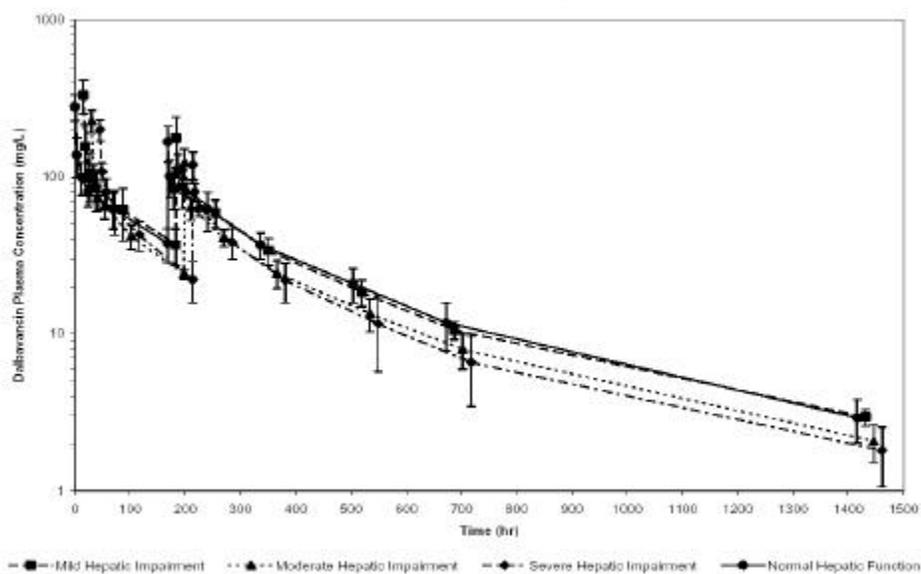
## Pharmacokinetic Results

### Plasma

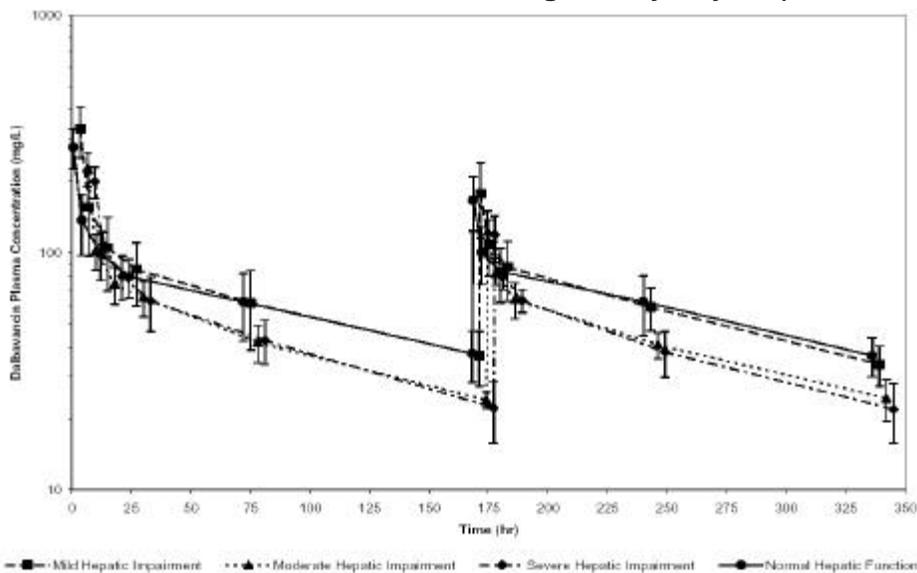
Fig 1 shows the mean ( $\pm$  sd) dalbavancin plasma concentration-time profile following administration of 1000 mg dalbavancin on day 1 and 500 mg dalbavancin on day 8 in subjects with various degrees of hepatic function.

**Fig 1: Mean ( $\pm$  SD) Dalbavancin Plasma Concentration-Time Profiles Following Administration of 1000 mg Dalbavancin on Day 1 and 500 mg Dalbavancin on Day 8 in Subjects with Various Degrees of Hepatic Function.**

#### A: Dalbavancin Concentrations through Study Day 60 (1416 hours)



#### B: Dalbavancin Concentrations through Study Day 15 (336 hours)



## Metabolite

Overall, all quantifiable OH-dalbavancin plasma concentrations were low and only just above the limit of quantification for the assay (LLOQ = 0.4 mg/L). The highest level of OH-dalbavancin observed was 2.19 mg/L for Subject 12001019 (normal hepatic function group) at 4 hours following the first dose.

## PHARMACOKINETIC DATA ANALYSIS RESULTS

### Dalbavancin

#### Plasma

Table 3 shows the summary of the PK parameters.

**Table 3: Mean ( $\pm$  SD) Dalbavancin Plasma Pharmacokinetic Parameters**

	Group A Mild Hepatic Impairment <sup>1</sup> (N=6)	Group B Moderate Hepatic Impairment <sup>2</sup> (N=6)	Group C Severe Hepatic Impairment <sup>3</sup> (N=5)	Group D Normal Hepatic Function (N=9)
<b>AUC<sub>0-24h</sub> (hr*mg/L)</b>	11146	7710	7561	10577
SD	3478	1099	1540	2493
%CV	31.21	14.25	20.37	23.57
<b>AUC<sub>0-48h</sub> (hr*mg/L)</b>	21158	14826	14112	20473
SD	5808	1925	2911	4883
%CV	27.45	12.99	20.63	23.85
<b>AUC<sub>0-inf</sub> (hr*mg/L)</b>	33117	23628	21639	33851
SD	6479	3527	5940	8184
%CV	19.57	14.93	27.45	24.18
<b>C<sub>max1</sub> (mg/L)</b>	331.7	227.2	199.0	278.3
SD	80.6	37.5	30.4	52.6
%CV	24.31	16.52	15.25	18.90
<b>C<sub>max2</sub> (mg/L)</b>	177.0	122.7	118.9	166.3
SD	62.4	27.2	23.9	42.9
%CV	35.25	22.18	20.09	25.77
<b>T<sub>max1</sub> (hr)<sup>4</sup></b>	0.53	0.52	0.54	0.52
Range	(0.52-0.55)	(0.52-0.53)	(0.52-0.63)	(0.52-0.53)
<b>T<sub>max2</sub> (hr)<sup>4</sup></b>	168.52	168.51	168.54	168.53
Range	(168.52-168.53)	(168.45-168.52)	(168.52-168.57)	(168.52-168.57)
<b>t<sub>1/2</sub> (hr)</b>	323	320	322	321
SD	27	24	68	24
%CV	8.45	7.34	21.07	7.32
<b>CL (L/hr)</b>	0.0466	0.0647	0.0736	0.0466
SD	0.0084	0.0098	0.0202	0.0110
%CV	17.98	15.22	27.40	23.70
<b>V<sub>ss</sub> (L)</b>	18.1	24.4	25.2	18.3
SD	5.2	3.0	4.0	3.7
%CV	28.65	12.47	15.74	20.19

Abbreviations: CV=coefficient of variation, SD=standard deviation, AUC=area under the plasma concentration curve, C<sub>max1</sub>=maximum observed plasma concentration after the first dose, C<sub>max2</sub>=maximum observed plasma concentration after the second dose, T<sub>max1</sub>=time of maximum observed plasma concentration, T<sub>max2</sub>=time of maximum observed plasma concentration, t<sub>1/2</sub>=terminal elimination half-life, CL=clearance, V<sub>ss</sub>=volume of distribution at steady state

<sup>1</sup> Mild hepatic function (Child-Pugh Class A – 5 to 6 points)

<sup>2</sup> Moderate hepatic impairment (Child-Pugh Class B – 7 to 9 points)

<sup>3</sup> Severe hepatic impairment (Child-Pugh Class C – 10 to 15 points)

<sup>4</sup> Values for T<sub>max</sub> represent Median (Range)

As the table indicates, the mean PK parameters for dalbavancin were similar between subjects with normal hepatic function and subjects with mild hepatic impairment. However, subjects with moderate hepatic impairment and subjects with severe hepatic impairment had decreased dalbavancin exposures. Furthermore, a trend towards increased clearance and volume of

distribution at steady state ( $V_{ss}$ ) was evident as the degree of hepatic impairment increased. Total clearance increased by 39 % and 58 % in subjects with moderate hepatic impairment and subjects with severe hepatic impairment, respectively. The half-life of dalbavancin remained relatively unchanged.

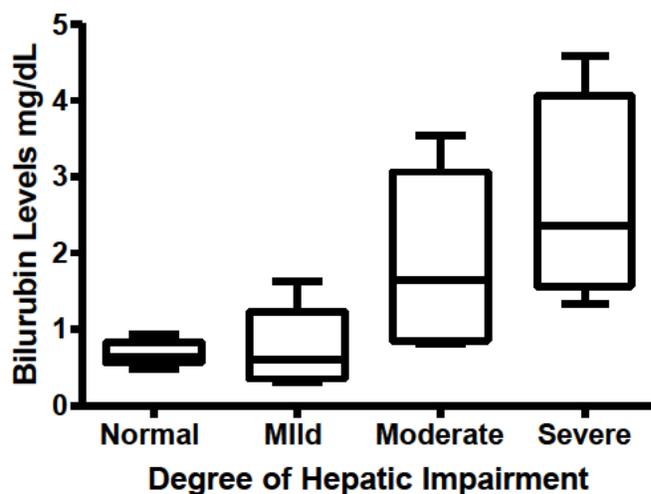
### OH-Dalbavancin

Overall, all quantifiable OH-dalbavancin plasma concentrations were low and only just above the limit of quantification (LLOQ 0.04  $\mu\text{g/mL}$ ) for the assay. Only 5 subjects (1 normal hepatic function, 1 mild hepatic impairment, 2 moderate hepatic impairment, and 1 severe hepatic impairment) had evaluable dalbavancin metabolite plasma concentration-time profiles, therefore no pharmacokinetic analysis was performed.

#### Reviewer's Comment Regarding Sponsor's Results

*The differences in clearance and volume of distribution (and hence the differences in exposures) can be explained, in part, on the basis of differences in bilirubin levels among the various treatment groups. Bilirubin may potentially compete with dalbavancin for the protein binding sites, thereby increasing the free fraction of dalbavancin. This will increase the clearance and volume of distribution to a similar extent (thereby keeping half-life unchanged) which may explain the differences in  $C_{max}$  and AUC. Fig 2 shows a box plot between the total bilirubin levels (computed as the sum of direct and indirect bilirubin) and the degree of hepatic impairment.*

**Fig 2: Relationship Between Bilirubin Levels and the Degree of Hepatic Impairment**



#### PHARMACOKINETIC CONCLUSIONS (As provided by the Sponsor)

- Concentration and exposures of dalbavancin did not increase with increasing degrees of hepatic impairment. Dalbavancin administration to subjects with normal hepatic function and subjects with mild hepatic impairment resulted in comparable concentration time profiles over the 60-day sampling interval.

- Dalbavancin administration to subjects with moderate hepatic impairment and subjects with severe hepatic impairment resulted in decreased observed concentrations when compared to subjects with normal hepatic function.
- The intersubject variability of PK parameters was low. Although dalbavancin PK parameters were statistically different between the higher and lower hepatic impairment groups, the ranges of exposure PK parameters significantly overlapped.
- Changes in dalbavancin pharmacokinetic parameters appeared to be influenced by the drug's distribution volume. Volume of distribution increased in a proportional or inversely proportional manner with CL, AUC, and  $C_{max}$ . It is likely that subjects with moderate and severe hepatic impairment, who may have ascites and edema, have larger volumes of drug distribution and subsequently slightly lower plasma exposures.
- The mean concentrations remained above 20 mg/L across all dose groups through the intended treatment duration of 14 days.

#### 4.2.14 A Phase I, open-label study to evaluate the safety, tolerability, and pharmacokinetics of intravenous Dalbavancin (VER001) in subjects with mild and moderate renal impairment and healthy subjects with normal renal function (VER001-13)

##### Sponsor

Vicuron Pharmaceuticals  
455, South Gulph Road, Suit 310  
King of Prussia, PA 19406.

##### Objectives

###### Primary

- The primary objective of the study was to investigate the safety, tolerability, and pharmacokinetics of dalbavancin in subjects with mild and moderate renal impairment compared to age-, gender-, and weight-matched healthy subjects with normal renal function.

###### Secondary

- If necessary, a secondary objective was to recommend a dosage adjustment for subjects with mild or moderate renal impairment.

##### Methodology

This was a Phase I, open-label, single-dose study of dalbavancin 1000 mg administered by intravenous (IV) infusion over 30 minutes to otherwise healthy subjects with mild and moderate renal impairment and to subjects with normal renal function.

Twenty-one (21) subjects = 18 to <80 years of age with varying degrees of renal function were enrolled in this study; 9 subjects in group A, 6 subjects in group B, and 6 subjects in group C. Table 1 provides the description of the various groups.

**Table 1: Treatment Groups in Study VER001-11**

Group	Renal Function	Creatinine Clearance
Group A	Normal renal function	Cl <sub>cr</sub> = 80 mL/min
Group B	Mild renal impairment	Cl <sub>cr</sub> 50 to 79 mL/min
Group C	Moderate renal impairment	Cl <sub>cr</sub> 30 to 49 mL/min

Subjects were assigned to one of the three groups based on their baseline estimated creatinine clearance values (CL<sub>cr</sub>). Creatinine clearance was estimated using serum creatinine concentration (C<sub>cr</sub>) obtained at screening and the Cockcroft-Gault formula using ideal body weight (IBW).

Subjects with mild renal impairment (Group B) were treated first. The safety and PK data (through day 14) in at least 4 subjects was reviewed by the sponsor to decide if Group C should receive the same or modified dalbavancin dosage. Control subjects with normal renal function were recruited throughout the study to match the enrolled renally impaired subjects with respect to age, weight, and gender.

## Inclusion/Exclusion Criteria

### Inclusion Criteria:

- Male or female = 18 years of age and < 80 years of age;
- Estimated CL<sub>cr</sub> of = 80 mL/min (normal renal function group), 50-79 mL/min (mild renal impairment group), or 30-49 mL/min (moderate renal impairment group);

### Exclusion Criteria:

- Creatinine clearance < 30 mL/min.
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times upper limit of normal.
- Total bilirubin > 2 times upper limit of normal.
- Had a transplanted kidney, heart, or liver.
- Urinary tract obstruction (e.g., prostatic hypertrophy) or urinary stasis.

## Investigational Product(s)

Dalbavancin was provided as a preservative-free, sterile, lyophilized, white to off-white powder in 20 mL single-use vials. Each vial contained 200 mg of dalbavancin, (b) (4) mannitol, and hydrochloric acid and/or sodium hydroxide for pH control. (Lot # 2050-09-285048).

## Drug Concentration Measurements

### Blood Collection

A total of 15 blood samples (10 mL each) were drawn at the following times: pre-infusion (blank sample), end of infusion (0.5 hours), and 1, 4, 8, and 16 hours post-start of infusion. In addition, blood samples were drawn on Days 2, 3, 4, 7, 14, 21, 28, 42, and 60

### Urine Collection

From days 1 through 3 (72 hours), 24-hour urine collections were done beginning immediately post-start of infusion. On Days 7, 14, 21, 28, 42, and 60, a single urine sample was collected. Two aliquots were retained from the sample obtained from each of these two days.

## Bioanalytical Measurements

Plasma and urine samples were assayed for dalbavancin and OH-dalbavancin using a validated liquid chromatography coupled to tandem-mass spectrometry (LC-MS/MS) method (b) (4). The LC-MS/MS method for dalbavancin and OH-dalbavancin was validated in the concentration linear range of 1-128 µg/mL for dalbavancin and 0.4-12.8 µg/mL for OH-dalbavancin. It was further extended to 240 µg/mL with a 10-fold dilution.

Overall precision for the quality control samples, as measured by percent relative standard deviation (% RSD) was = 8.48 % for dalbavancin and = 18.8 % for OH-dalbavancin. Overall accuracy, as measured by absolute percent relative error (% RE), for these quality control samples ranged from 1-10.5 % for dalbavancin and 0-9.4 % for OH-dalbavancin. Overall

precision and accuracy for the dilution integrity quality control samples was 4.79 % for dalbavancin. Overall accuracy for the dilution integrity quality control plasma samples was 0.833 for dalbavancin.

Overall precision for the quality control urine samples, as measured by % RSD, was = 6.88 % for dalbavancin and = 10.7 % for OH-dalbavancin. Overall accuracy, as measured by % RE, for these quality control samples ranged from 0.8 % to 9.33 % for dalbavancin and 11.0 % to 17.0 % for OH-dalbavancin.

## Pharmacokinetic Parameter Calculations

### Plasma

Dalbavancin and OH-Dalbavancin plasma and urine pharmacokinetic parameters were estimated using noncompartmental techniques (*Winnonlin™ Professional Network Edition, Version 4.0.1, Pharsight Corp, Palo Alto, CA*). All measurements below the limit of quantitation (BQL) and no results (NR) values occurring at the end of the data set were treated as missing and appear in the data set as ".". All BQL and NR values occurring at the beginning of the data set prior to time to maximum plasma concentration ( $T_{max}$ ) were replaced by "0" instead of being treated as missing.

$C_{max}$  and  $T_{max}$  were obtained directly from the observed data.  $AUC_{0-t}$  (where t is day 7, Day 14, or last {time of last concentration}) was calculated using the log-linear trapezoidal rule. The area under the plasma concentration-time curve extrapolated to infinity ( $AUC$  or  $AUC_{0-inf}$ ) was calculated as the sum of  $AUC_{0-last}$  and  $C_{last}/\text{terminal elimination rate constant } (\lambda_z)$ . The elimination half life ( $t_{1/2}$ ) was estimated by linear regression of the log-linear portion of the log concentration versus time curve.  $CL$  was computed as  $\text{dose}/AUC_{0-inf}$ . The volume of distribution at steady state ( $V_{ss}$ ) was calculated from the area under the first moment curve (AUMC) multiplied by the dose and divided by the  $AUC$  squared.

### Urine

The area under the urinary excretion rate curve (AURC) was calculated using the linear trapezoidal rule. The cumulative amount of dalbavancin excreted in urine was estimated as the AURC. The renal clearance ( $CL_r$ ) was calculated as the ratio:  $CL_{cr} = AURC_{0-last}/AUC_{0-last}$ . The non-renal clearance,  $CL_{nr}$ , was calculated as the difference between  $CL$  and  $CL_r$ .

## STUDY SUBJECTS

### Disposition

Table 1 shows the disposition of subjects in each treatment group that enrolled, discontinued and completed the study by treatment group.

**Table 1: Number of Subjects Enrolled, Discontinued, and Completed**

	Renal Function (Study Group)		
	Normal (A)	Mild Impairment (B)	Moderate Impairment (C)
Enrolled	9	6	6
Discontinued	0	0	0
Completed	100%	100%	100%

Protocol Deviations

There were no protocol deviations leading to exclusion from the analyses.

**Demographics and Other Baseline Characteristics**

Table 2 shows the demographic and baseline characteristics for the study population.

**Table 2: Demographics and Baseline Characteristics**

Characteristic	Renal Function, Study Group		
	Group A Normal (N = 9)	Group B Mild Impairment (N = 6)	Group C Moderate Impairment (N = 6)
Age, mean ± SD (yrs)	57.2 ± 15.4	57.2 ± 12.5	69.0 ± 7.6
Height, mean ± SD (cms)	179.5 ± 10.5	173.3 ± 5.2	163.1 ± 6.3
Weight, mean ± SD (kg)	83.1 ± 12.7	77.8 ± 7.9	77.7 ± 17.0
Study CL <sub>cr</sub> <sup>1</sup> mean ± SD (mL/min)	96.8 ± 22.6	64.0 ± 9.6	39.0 ± 8.0
CL <sub>cr</sub> (IBW) <sup>2</sup> mean ± SD (mL/min)	91.6 ± 26.4	64.0 ± 9.6	37.8 ± 6.0
CL <sub>cr</sub> (ABW) <sup>3</sup> mean ± SD (mL/min)	104.8 ± 24.2	73.7 ± 13.0	52.8 ± 13.2
CL <sub>cr</sub> on Day 1-2 mean ± SD (mL/min)	101.2 ± 21.6	65.2 ± 21.5	44.1 ± 12.6

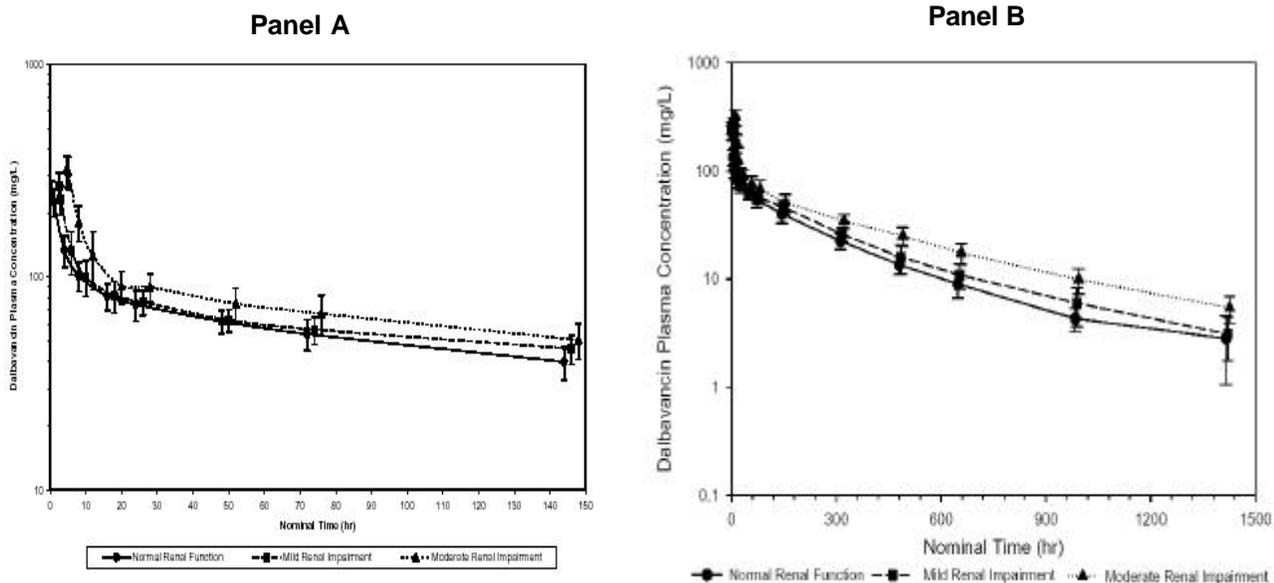
<sup>1</sup> Study CL<sub>cr</sub> was the CL<sub>cr</sub> that was used as entrance criteria for the study in all pharmacokinetic analysis.

<sup>2</sup> CL<sub>cr</sub> was calculated using the Cockcroft-Gault formula using serum creatinine levels and ideal body weight (IBW). <sup>3</sup> CL<sub>cr</sub> was calculated using the Cockcroft-Gault formula using serum creatinine levels and actual body weight (ABW).

**Pharmacokinetic Results**Plasma

Fig 1 shows the mean (± sd) dalbavancin plasma concentration-time profile following administration of a single 1000 mg IV dose of dalbavancin in subjects with normal renal function, mild renal impairment, or moderate renal impairment. The profiles are presented on two time scales: 0-150 hours (panel A) and 0-150 hours (panel B).

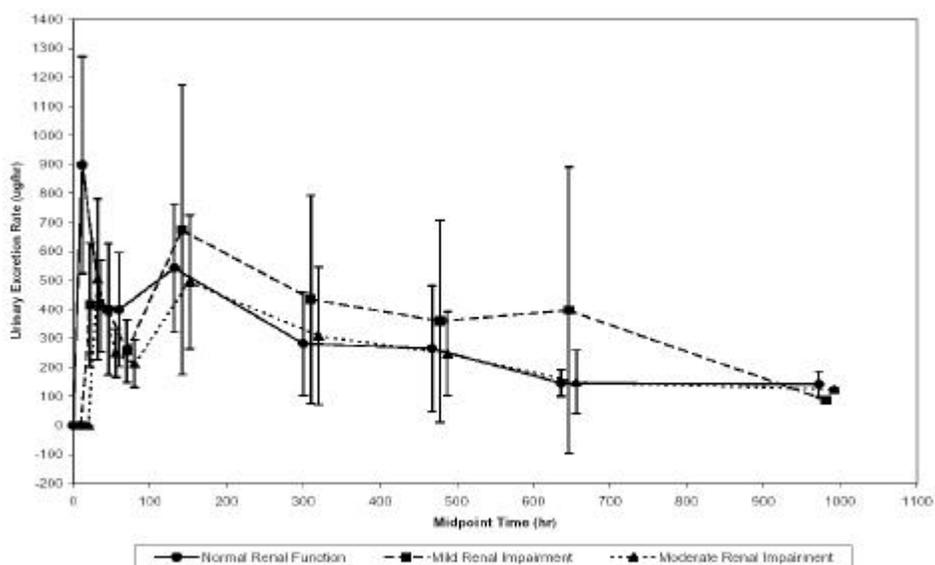
**Fig 1: Mean ( $\pm$  SD) Dalbavancin Plasma Concentration-Time Profiles Following Administration of 1000 mg Dalbavancin in Subjects with Normal Renal Function, Mild Renal Impairment, or Moderate Renal Impairment. The profiles are presented on two time scales: 0-150 hours (panel A) and 0-1500 hours (panel B).**



## Urine

Fig 2 shows the mean ( $\pm$  SD) dalbavancin urinary excretion rate-time profiles following administration of 1000 mg dalbavancin in subjects with normal renal function, mild renal impairment, or moderate renal impairment.

**Fig 2: Mean ( $\pm$  SD) Dalbavancin Urinary Excretion Rate-Time Profiles Following Administration of 1000 mg Dalbavancin in Subjects with Normal Renal Function, Mild Renal Impairment, or Moderate Renal Impairment.**



## OH-Dalbavancin

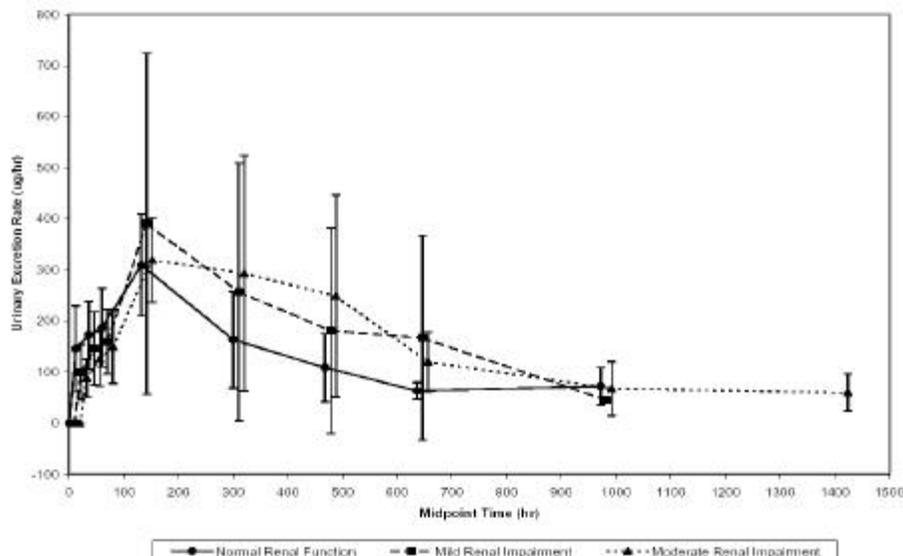
### Plasma

Of the 9 subjects with normal renal function (Study Group A), no subjects had quantifiable levels of OH-dalbavancin over the duration of the study. Of the 6 subjects with mild renal impairment (Study Group B), only 2 subjects had quantifiable levels of OH-dalbavancin. Of the 6 subjects with moderate renal impairment (Study Group C), 4 subjects had quantifiable levels of OH-dalbavancin. All quantifiable OH-dalbavancin plasma concentrations were low and only just above the limit of quantitation for the assay (LLOQ = 0.4  $\mu$ g/mL). The highest level of OH-dalbavancin observed was 0.7 mg/L for one subject in the moderate renal impairment group at 72 hours following the dose.

### Urine

Fig 3 shows the mean (SD) OH-Dalbavancin urinary excretion rate-time profiles following administration of 1000 mg dalbavancin in subjects with normal renal function, mild renal impairment, or moderate renal impairment.

**Fig 3: Mean (SD) OH-Dalbavancin Urinary Excretion Rate-Time Profiles Following Administration of 1000 mg Dalbavancin in Subjects with Normal Renal Function, Mild Renal Impairment, or Moderate Renal Impairment**



## PHARMACOKINETIC DATA ANALYSIS RESULTS

### Dalbavancin

#### Plasma

Table 3 shows the summary of the PK parameters. The mean pharmacokinetic parameters for dalbavancin were similar between subjects with normal renal function (Study Group A) and subjects with mild renal impairment (Study Group B). Subjects with moderate renal impairment (Study Group C) had an approximately 50 % increase in  $AUC_{0-inf}$  compared to subjects with normal renal function. However, comparison of  $AUC_{0-day7}$  and  $AUC_{0-day14}$  between study groups showed only a respective 23 % and 31 % increase in exposure. Dalbavancin CL and  $V_{ss}$  appeared to decrease as the degree of renal impairment increased. Mean CL was 35 % lower in subjects with moderate renal impairment compared to subjects with normal renal function. Mean  $V_{ss}$  was 21 % lower for subjects with moderate renal impairment. Terminal half life was relatively unchanged across the groups.

**Table 3: Mean ( $\pm$  SD) Dalbavancin Plasma Pharmacokinetic Parameters**

	<b>Group A Normal Renal Function<sup>1</sup> (N = 9)</b>	<b>Group B Mild Renal Impairment<sup>2</sup> (N = 6)</b>	<b>Group C Moderate Renal Impairment<sup>3</sup> (N = 6)</b>
<b>AUC<sub>0-day7</sub> (hr*mg/L)</b>	8992 (1362)	9714 (1406)	11050 (2005)
<b>AUC<sub>0-day14</sub> (hr*mg/L)</b>	13765 (1986)	15333 (1884)	18060 (3065)
<b>AUC<sub>0-inf</sub> (hr*mg/L)</b>	24561 (5252)	27047 (4084)	37665 (7123)
<b>C<sub>max</sub> (mg/L)</b>	248.8 (33.0)	266.8 (42.3)	330.7 (55.7)
<b>T<sub>max</sub> (hr)<sup>4</sup></b>	0.50 (Range: 0.42-1.00)	0.50 (Range: 0.50 – 0.55)	0.56 (Range: 0.50 – 1.22)
<b>V<sub>SS</sub> (L)</b>	18.5 (3.6)	16.5 (3.3)	14.7 (2.1)
<b>CL (L/hr)</b>	0.0422 (0.0079)	0.0376 (0.0048)	0.0273 (0.0045)
<b>t<sub>1/2</sub> (hr)</b>	417 <sup>5</sup> (108)	389 (59)	432 (43)

The results from regression analysis suggested that C<sub>max</sub> and AUC were higher among subjects with lower creatinine clearance and CL was correlated with creatinine clearance. The slope estimate absolute ratios to SE are greater than 4 (p<0.001) for AUC<sub>0-inf</sub> and CL. Table 4 shows the regression analysis results.

**Table 4: Results of Regression Analysis of Selected Dalbavancin Plasma Pharmacokinetic Parameters**

Parameter	Regression Coefficients	Group A	Group B	Group C
Median CLcr (mL/min)		86	61.1	38.75
C <sub>max</sub> (ng/L)				
Intercept, ln of parameter	5.9			
Slope (SE)	-0.0037(0.0012)			
Predicted (95% CI, ln scale)		5.552 (5.466, 5.637)	5.604 (5.565, 5.722)	5.725 (5.613, 5.838)
Predicted (95% CI, orig scale)		258(237, 281)	282(261, 306)	307(274, 343)
AUC <sub>0-7</sub> (hr*ng/L)				
Intercept, ln of parameter	9.4			
Slope (SE)	-0.0027(0.0012)			
Predicted (95% CI, ln scale)		9.134 (9.05, 9.217)	9.2 (9.122, 9.278)	9.26 (9.149, 9.371)
Predicted (95% CI, orig scale)		9261(8519, 10068)	9900(9156, 10704)	10510(9405, 11744)
AUC <sub>0-14</sub> (hr*ng/L)				
Intercept, ln of parameter	9.9			
Slope (SE)	-0.0034(0.0012)			
Predicted (95% CI, ln scale)		9.577 (9.499, 9.656)	9.663 (9.589, 9.736)	9.739 (9.634, 9.844)
Predicted (95% CI, orig scale)		14436(13341, 15622)	15720(14601, 16924)	16969(15279, 18846)
AUC <sub>0-last</sub> (hr*ng/L)				
Intercept, ln of parameter	10.6			
Slope (SE)	-0.0057(0.0012)			
Predicted (95% CI, ln scale)		10.08 (9.996, 10.165)	10.222 (10.143, 10.301)	10.35 (10.237, 10.462)
Predicted (95% CI, orig scale)		23866(21929, 25975)	27506(25412, 29772)	31243(27917, 34965)
AUC <sub>0-inf</sub> (hr*ng/L)				
Intercept, ln of parameter	10.7			
Slope (SE)	-0.006(0.0014)			
Predicted (95% CI, ln scale)		10.153 (10.058, 10.249)	10.303 (10.214, 10.392)	10.438 (10.311, 10.564)
Predicted (95% CI, orig scale)		25680(23349, 28243)	29829(27290, 32605)	34122(30067, 38723)

Renal Impairment Groups: (A) Normal Renal Function CLcr $\geq$ 80 mL/min; (B) Mild CLcr 50 to 79 mL/min; (C) Moderate CLcr 30 to 49 mL/min.

## Urine

Table 5 shows the summary statistics of the dalbavancin urine pharmacokinetic parameters by study group. On average, the urinary excretion of dalbavancin was comparable across groups.  $AURC_{0-last}$  was used as an estimate of the total amount of dalbavancin excreted in the urine and  $CL_r$  was calculated as  $AURC_{0-last}/AUC_{0-last}$ . The estimated fraction of dalbavancin excreted in the urine was approximately 20-25 % of the total dose administered, based on  $AURC_{0-last}$  calculation.

**Table 5: Mean ( $\pm$  SD) Dalbavancin Pharmacokinetic Parameters**

	Normal Renal Function <sup>1</sup> (N = 9)	Mild Renal Impairment <sup>2</sup> (N = 6)	Moderate Renal Impairment <sup>3</sup> (N = 6)
$AURC_{0-last}$ (hr <sup>3</sup> mg/hr)	199.3 (116.0)	250.4 (212.2)	188.1 (101.0)
% CV	58.22	84.75	53.67
$CL_r$ (L/hr)	0.00871 (0.00470)	0.01037 (0.00894)	0.00541 (0.00226)
% CV	53.94	86.21	41.77
$CL_{ur}$ (L/hr)	0.0335 (0.0095)	0.0272 (0.0074)	0.0218 (0.0055)
% CV	28.27	27.20	24.96

<sup>1</sup>: Normal renal function ( $CL_{cr} > 80$  mL/min)

<sup>2</sup>: Mild renal impairment ( $CL_{cr}$  Range 50-79 mL/min)

<sup>3</sup>: Moderate renal impairment ( $CL_{cr}$  Range 30-49 mL/min)

## OH-Dalbavancin

### Plasma

Only 2 subjects with moderate renal impairment had evaluable OH-dalbavancin plasma concentration-time profiles. All quantifiable OH-dalbavancin plasma concentrations were low and only just above the limit of quantification of the assay (LLQ = 0.4  $\mu$ g/mL).

### Urine

The mean OH-dalbavancin urine pharmacokinetic parameters were similar among study groups. Based on the  $AURC_{(m) 0-last}$ , approximately 10-20 % of the dose was excreted as the OH-dalbavancin metabolite.

## PHARMACOKINETIC CONCLUSIONS (As provided by the sponsor)

- Dalbavancin administration to subjects with normal renal function and subjects with mild renal impairment resulted in comparable concentration-time profiles and exposures over the 60-day sampling interval.
- The first 7 to 14 days post-dose are considered to be the effective treatment period of the drug. Through 14 days post-dose, dalbavancin plasma concentrations were comparable

among subjects with normal renal function and subjects with mild or moderate renal impairment. An increased concentration was observed in subjects with moderate renal impairment beyond Day 14, at a point in the profile when concentrations were below 40 mg/L.

- A trend towards an increase in dalbavancin exposure and a decrease in CL was evident for subjects with moderate renal impairment.
- Daalbavancin and OH-Dalbavancin metabolite was excreted in the urine. Across all groups, approximately 20-25 % of the dose was excreted as dalbavancin and 10-20 % as the OH metabolite. Together, urinary excretion accounted for approximately 30-45 % of the dose. Although limitations in the urinary sampling schemes did not allow for an accurate estimation of  $CL_r$ , there was a trend towards reduction in renal clearance in subjects with moderate renal impairment.

#### 4.2.15 A phase 1 study to evaluate the distribution and excretion of intravenous dalbavancin in healthy subjects after a single dose (Study VER001-19)

Dates: March 3, 2004 to May 16, 2004

Clinical site: MDS Pharma Services, Lincoln, NE 68502

Analytical site: (b) (4) (plasma, urine, skin blister fluid samples); Vicuron Pharmaceuticals, 21040 Gerenzano (Varese) - Italy (fecal samples)

##### **OBJECTIVES:**

The primary objective of this study was to investigate the excretion of dalbavancin in healthy subjects. The secondary objectives were to determine the penetration of dalbavancin into skin blister fluid with respect to drug plasma concentrations and to further evaluate the safety profile of dalbavancin.

##### **FORMULATIONS:**

Dalbavancin lyophilized powder, 200 mg/vial (Lot No. 2050-09-285048, Batch No. 20381A0, (b) (4))

##### **STUDY DESIGN:**

This was a single center, open-label, single-dose study of 1000 mg dalbavancin administered IV as a 30 min infusion to nine healthy subjects aged 19 to 65 yrs. The study duration was up to 10 weeks after administration of a single dose of study drug. Subjects were housed in the clinical research unit through the first 7 days following dosing and returned for a 24-hr observation and collection period on Days 14, 21, 28, 42, 56, and 70.

##### **Blood collection**

Blood samples for determination of plasma dalbavancin and OH-dalbavancin concentrations were obtained at predose, end of infusion ( $\pm 15$  min), 4 and 12 hrs post start of infusion ( $\pm 30$  min), and on days 2, 3, 7, 14, 21, 28, 42, 56, 70 ( $\pm 3$  days). Blood was collected from each subject for the assessment of dalbavancin, and OH-dalbavancin, and other possible metabolites in plasma. Actual sample times were 0, 0.75, 4.5, 12.5, 24, 48, 144, 312, 480, 648, 984, 1320, and 1656 hrs.

##### **Urine collection**

On days 1 through 8 (0 to 168 hrs), 24-hr urine collections were obtained. Additional 24-hr urine collections were collected on days 14, 21, 28, 42, 56, and 70 ( $\pm 3$  days) when subjects returned to the clinic and remained confined during this time. Actual sample times on days 14 to 70 were 312 to 336, 480 to 504, 648 to 672, 984 to 1008, 1320 to 1344, and 1608 to 1632 hrs.

##### **Fecal collection**

Within 3 days prior to the dalbavancin infusion, each subject was to have a fecal sample collected. On days 1 through 8, 24-hr fecal collections were obtained. Additional 24-hr fecal collections were performed on days 14, 21, 28, 42, 56, and 70 ( $\pm 3$  days) when subjects returned to the clinic and remained confined during this time.

##### **Skin blister fluid collection**

On days 1, 3, 5, and 7, fluid samples from cantharidin-induced skin blisters were obtained. The first blister was induced on the ulnar surface of the forearm of the subjects approximately 12 to 14 hrs prior to study drug infusion on day -1. A second blister was induced prior to drug administration on day 1 and fluid was drawn 12 hrs following the start of the infusion on Day 1. Additional blisters were induced on the forearm of the subjects 12 to 14 hrs prior to collection on study days 3, 5, and 7 approximately  $\pm 30$  min relative to initiation of drug infusion on day 1.

**DALBAVANCIN ASSAY METHODOLOGY:**

High performance liquid chromatography with mass spectrometric detection (LC/MS/MS)

Criterion	Plasma	Urine	Blister fluid	Comments
Concentration range	1 to 128 µg/mL	1 to 128 µg/mL	1 to 128 µg/mL	Satisfactory
LLOQ	1 µg/mL	1 µg/mL	1 µg/mL	Satisfactory
Linearity	$R^2 \geq 0.9920$	$R^2 \geq 0.9934$	$R^2 = 0.9971$	Satisfactory
Accuracy	97.3% to 102.0%	96.6% to 115.7%	100.7% to 116.1%	Satisfactory
Precision	5.9% to 14.4%	4.8% to 8.3%	9.9% to 10.3%	Satisfactory
Specificity	Acceptable	Acceptable	Acceptable	Satisfactory
Stability	Freeze-thaw, long term at -20°C	Freeze-thaw, long term at -20°C	Not stated	Satisfactory

**OH-DALBAVANCIN ASSAY METHODOLOGY:**

High performance liquid chromatography with mass spectrometric detection (LC/MS/MS)

Criterion	Plasma	Urine	Blister fluid	Comments
Concentration range	0.4 to 12.8 µg/mL	0.4 to 12.8 µg/mL	0.4 to 12.8 µg/mL	Satisfactory
LLOQ	0.4 µg/mL	0.4 µg/mL	0.4 µg/mL	Satisfactory
Linearity	$R^2 \geq 0.9819$	$R^2 \geq 0.9762$	$R^2 = 0.9943$	Satisfactory
Accuracy	112.0% to 119.0%*	101.0% to 115.0%	90.6% to 106.7%	Satisfactory
Precision	2.1% to 17.9%*	7.2% to 15.4%	14.2% to 22.1%	Satisfactory
Specificity	Acceptable	Acceptable	Acceptable	Satisfactory
Stability	Freeze-thaw, long term at -20°C	Freeze-thaw, long term at -20°C	Not stated	Satisfactory

\* LLOQ

A partial validation using standards and quality controls prepared in blister fluid was successfully performed for dalbavancin prior to sample analysis. However, the partial validation was not fully successful for OH-dalbavancin and limited availability of matrix precluded further evaluation. Thus, the results should be interpreted as estimates only.

**DALBAVANCIN ASSAY METHODOLOGY:**Agar diffusion microbiological assay with *B. subtilis* ATCC 6633 as the test organism

Criterion	Fecal	Comments
Concentration range	0.05 to 3.2 µg/mL	Satisfactory
LLOQ	0.05 µg/mL	Satisfactory
Linearity	$R^2 \geq 0.9713$	Satisfactory
Accuracy	83.8% to 97.3%	Satisfactory
Precision	5.3% to 10.8%	Satisfactory
Specificity	Not stated	Unsatisfactory
Stability	Freeze-thaw, short term at room temp, extracted stability at 4°C	Satisfactory

**PHARMACOKINETIC ANALYSIS:**

Dalbavancin and OH-dalbavancin plasma, urine, and feces pharmacokinetic parameters were estimated by noncompartmental methods using WinNonlin™ Version 4.0 (Pharsight Corporation). The estimated pharmacokinetic parameters included the maximum concentration of study drug in plasma ( $C_{max}$ ), the time of maximum concentration ( $T_{max}$ ), both obtained directly from the observed data; apparent terminal elimination half-life ( $t_{1/2}$ ), the area under the plasma concentration-time curve determined using the linear

trapezoidal method ( $AUC_{0-t}$ ,  $AUC_{0-144}$ , and  $AUC_{0-\infty}$ ), plasma clearance ( $CL_T$ ), and volume of distribution at steady-state ( $V_{SS}$ ).

The cumulative amount of dalbavancin and OH-dalbavancin excreted in urine was determined as the integrand of the area under the urine excretion rate curve (AURCurine) through the last measurable sample. The renal clearance ( $CL_R$ ) was calculated at the ratio of (AURCurine/AUC) for both dalbavancin and OH-dalbavancin.

For feces, the cumulative amount of dalbavancin excreted in feces was determined as the integrand of the area under the fecal excretion rate curve (AURCfeces) through the last measurable sample.

The  $C_{max}$  in skin blister fluid and  $T_{max}$  were determined directly from the data. The AUC was determined by the trapezoidal method. The degree of penetration of dalbavancin into the skin was determined by the ratio of the AUC of skin blister fluid through Day 7 to the AUC of plasma through Day 7.

#### STATISTICAL ANALYSIS:

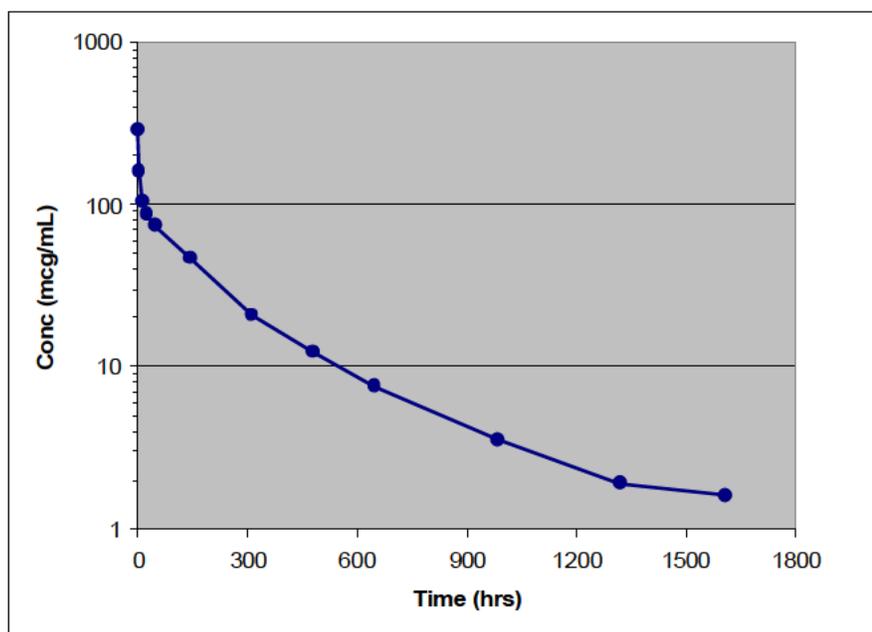
Descriptive statistics were used to analyze the pharmacokinetic parameters. No formal statistical comparisons were made.

#### RESULTS:

Nine subjects were enrolled, received study medication, and completed the study. The mean (SD) age, height, and weight were 41.2 (12.6) yrs, 173.8 (10.5) cm, and 77.5 (10.0) kg, respectively. Four subjects were female, five subjects were male, and eight of the subjects were Caucasian.

The mean plasma concentration-time profile of dalbavancin following a single dose of 1000 mg infused over 30 min is shown in Figure 1. Maximum plasma concentrations ( $C_{max}$ ) were reached at the end of infusion and the mean  $C_{max}$  was 285  $\mu\text{g/mL}$ . At 144 hrs following administration (end of day 6), the mean plasma concentration was 46.5  $\mu\text{g/mL}$  and ranged from 38.1 to 67.2  $\mu\text{g/mL}$ .

**Figure 1. Mean plasma dalbavancin concentration-time profile following administration of a single dose of dalbavancin 1000 mg**



The mean (CV%) plasma and urine pharmacokinetic parameters of dalbavancin following administration of 1000 mg dalbavancin IV are shown in Table 1. The mean  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were 24,248  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and 25,088  $\mu\text{g}\cdot\text{hr}/\text{mL}$ , respectively; less than 4% of the exposure was extrapolated.

Overall, the mean pharmacokinetic parameters were similar to the values reported in Study VER001-10. However, the mean elimination half-life from the current study (372 hrs) was appreciably longer than the range of values reported in Study VER001-2 (149 to 189 hrs) and the mean value reported in Study VER001-10 (261 hrs). In addition, the mean  $CL_R$  and urinary recovery of dalbavancin were approximately 58% of the values previously reported in Study VER001-10.

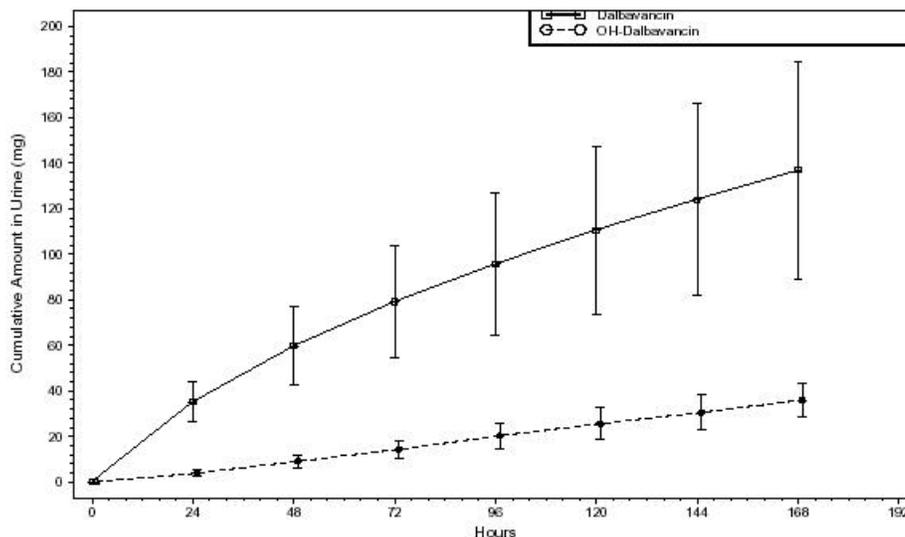
The sponsor stated that the longer half-life estimated in this study (14 - 17 days) compared to Study VER001-10 (8 - 13 days) was due to the longer sampling used in the present study (through Day 70) compared to day 42 in the previous study. When the reviewer calculated the half-lives in the current study out to day 42 (144 to 984 hrs), the mean half-life was 232 hrs and ranged from 190 to 290 hrs. In comparison, the half-life from Study VER001-10 was 261 hrs. It appears that the half-life is dependent upon the sampling interval and provides evidence that dalbavancin likely distributes to a deep tissue compartment.

**Table 1. Mean (CV%) pharmacokinetic of dalbavancin and OH-dalbavancin parameters following a single 1000 mg dose of dalbavancin infused over 30 min**

Parameter	Dalbavancin	OH-Dalbavancin
$C_{\max}$ ( $\mu\text{g}/\text{mL}$ )	285 (11%)	BLOQ
$AUC_{0-144}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	10,806 (18%)	BLOQ
$AUC_{0-t}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	24,248 (14%)	BLOQ
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	25,088 (15%)	BLOQ
$CL_T$ (L/hr)	0.0405 (13%)	BLOQ
$V_{SS}$ (L)	13.8 (17%)	BLOQ
$t_{1/2}$ (hrs)	372 (7%)	BLOQ
$CL_R$ (L/hr)	0.0081 (42%)	BLOQ
Urinary excretion in 24 hrs (mg)	35.0	3.8
Urinary excretion in 168 hrs (mg)	136.8	35.9
Urinary excretion extrapolated to 1632 hrs (mg)	192 (35%)	77.9 (15%)

The concentrations of the primary metabolite of dalbavancin (OH-dalbavancin) in plasma were below the lower limit of quantitation (LLOQ) of 0.4  $\mu\text{g}/\text{mL}$  in all subjects at all time points. However, OH-dalbavancin concentrations were quantifiable in urine. The cumulative amounts of dalbavancin and OH-dalbavancin excreted in urine are shown in Figure 2. The estimated fraction of the dose excreted unchanged in the urine was approximately 19% for dalbavancin and approximately 8% for OH-dalbavancin. At the end of 7 days (168 hrs), approximately 13.7% and 3.6% of the administered dose was excreted as unchanged dalbavancin and OH-dalbavancin, respectively. The urine concentrations of dalbavancin and OH-dalbavancin remained above the LLOQ in 3/9 subjects by day 21 and 4/9 subjects by day 28, respectively.

**Figure 2. Mean cumulative amount of dalbavancin and OH-dalbavancin excreted in urine vs. time following administration of a single dose of dalbavancin 1000 mg**

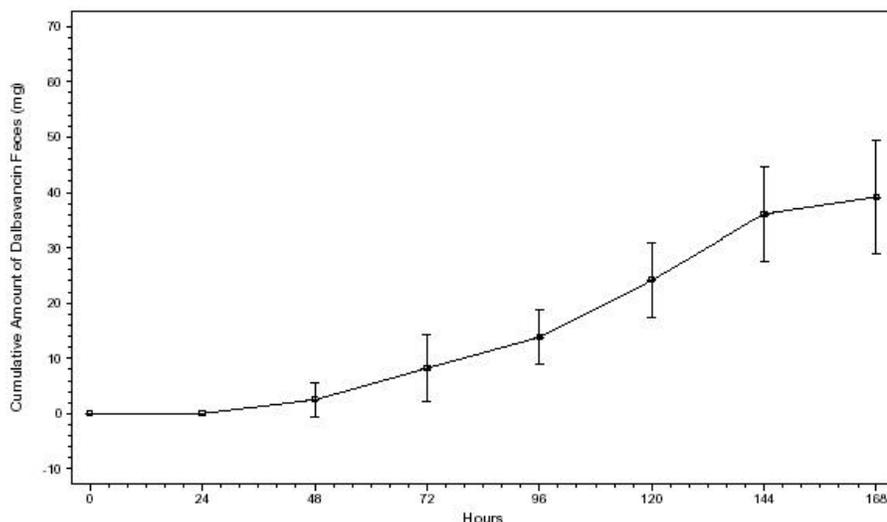


The amount of drug excreted in urine as either dalbavancin or OH-dalbavancin appeared to be lower in the current study compared to Study VER001-10. In that study, approximately 33% and 12% of the dose excreted into urine as dalbavancin and OH-dalbavancin, respectively. The sponsor states that this is explained by the different assay used in the previous study, which had a LLOQ of 0.5  $\mu\text{g/mL}$  (for dalbavancin and OH-dalbavancin) compared to 1  $\mu\text{g/mL}$  used in this study. The LLOQ in the current study was 1.0  $\mu\text{g/mL}$  for dalbavancin and 0.4  $\mu\text{g/mL}$  for OH-dalbavancin and does not explain the discrepancy in the urinary excretion between the two studies.

The reviewer calculated the amount of dalbavancin and OH-dalbavancin excreted in urine over 1632 hrs. The amount of dalbavancin and OH-dalbavancin were calculated by integrating the average urinary excretion rate (mg per hr) at the midpoint time of the urine collection interval over the entire urine collection period (1632 hrs). The mean urinary excretion of dalbavancin and OH-dalbavancin calculated by the reviewer was 214.5 mg and 84.2 mg, respectively compared to 192 mg and 77.9 mg, respectively reported by the sponsor. Although the reviewer's calculations increase the amount of dalbavancin and OH-dalbavancin excreted in urine, the values are well below those reported in Study VER001-10.

The mean cumulative amount of dalbavancin excreted in the feces vs. time through the first week (168 hrs) is shown in Figure 3. By day 21, the concentrations of dalbavancin in feces were above the LLOQ in 6/9 subjects. Approximately 39 mg (4% of the administered dose) was recovered in feces after 168 hrs. The estimated fraction of drug excreted in the feces was approximately 20% of the administered dose and ranged from 5% to 60%.

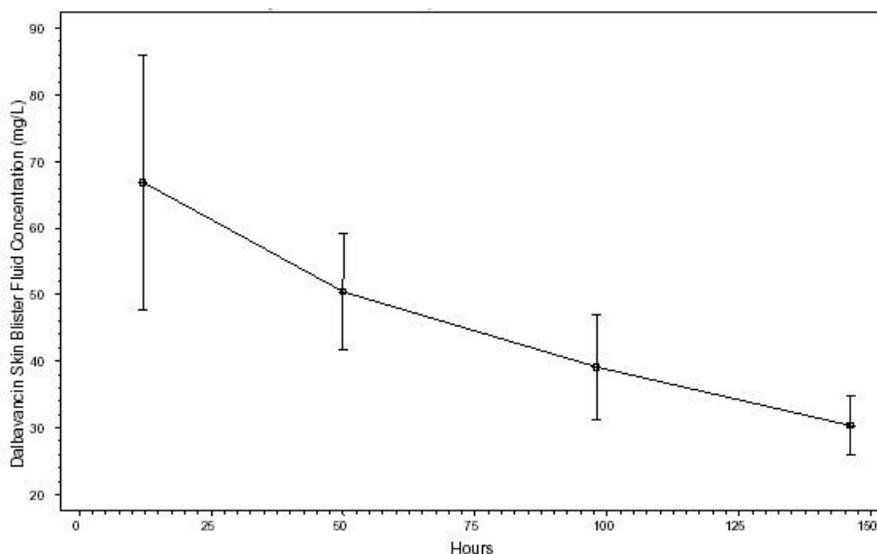
**Figure 3. Mean cumulative amount of dalbavancin excreted in feces vs. time following administration of a single dose of dalbavancin 1000 mg**



The mean concentration-time profile of dalbavancin in skin blister fluid is shown in Figure 4. The sponsor performed a partial-validation of dalbavancin and OH-dalbavancin in blister fluid. Only a single standard curve was performed in duplicate; thus, an intra-day and inter-day validation has not been performed and the reported concentrations should be used for information purposes only.

The mean dalbavancin blister fluid concentration remained above 30  $\mu\text{g/mL}$  through 146 hrs (range 19.7 to 34.0  $\mu\text{g/mL}$ ). The lowest reported concentration was 19.7  $\mu\text{g/mL}$  (Subject 190011 on Day 7) and the highest concentration was 102  $\mu\text{g/mL}$  (Subject 190017 at 12 hrs). The mean (SD) AUC in blister fluid through day 7 was 6438 (1238)  $\mu\text{g}\cdot\text{hr/mL}$ . The mean penetration of dalbavancin into skin blister fluid calculated as the  $\text{AUC}_{\text{blister fluid}}/\text{AUC}_{\text{plasma}}$  through day 7 was 60% (range 44% to 64%). The concentrations of OH-dalbavancin in blister fluid were below the LLOQ at all time points except at 50 hrs from one subject.

**Figure 4. Mean dalbavancin blister fluid concentration-time profile following administration of a single dose of dalbavancin 1000 mg**



Although the protein binding of dalbavancin in skin blister fluid is unknown, it is likely to be lower than the protein binding in plasma. Since the mean blister fluid concentration of dalbavancin at 7 days post-dose was 30.3 µg/mL (ranged from 19.7 to 34.0 µg/mL), the concentration of dalbavancin in interstitial fluid will likely exceed the proposed susceptibility breakpoints for *S. aureus* and *Streptococcus* spp. (MIC (b) (4) respectively) even if the protein binding is the same in interstitial fluid as in plasma (93%).

**SAFETY:**

There were no deaths, life-threatening adverse events (AEs), serious AEs (SAEs), premature discontinuations from study, or discontinuation of study drug due to AEs. All nine subjects reported at least one treatment emergent AE, the majority of which (20/23, 87%) were mild in intensity. The remaining 3 AEs (13%) were moderate in intensity. The most frequently reported AEs were infusion site pain (four subjects), followed by infusion site erythema, headache, and sinus congestion (two subjects each).

Two subjects exhibited abnormal serum chemistry values. Subject 190011 had an elevated calcium value of 14.6 mg/dL at post study and Subject 190017 exhibited a decreased potassium value of 3.7 mEq/L at post study. No subject had an elevation of liver function enzymes.

**CONCLUSIONS:**

1. Plasma concentrations of dalbavancin exceeded 40 µg/mL (total plasma concentrations) through 6 days (144 hrs) following a single 1000 mg IV dose of dalbavancin infused over 30 min.
2. Excretion of unchanged dalbavancin into urine accounted for 19% of the administered dose and excretion of OH-dalbavancin in urine accounted for 8% of the administered dose. Excretion of unchanged drug into feces accounted for 20% of the administered dose.
3. Dalbavancin penetrated into skin blisters with a blister fluid relative exposure of 60% compared to plasma.

**COMMENTS:**

1. The sponsor stated that blood samples were analyzed for evaluation of dalbavancin and possible metabolites of dalbavancin, including OH-dalbavancin. However, the sponsor only reported the results of OH-dalbavancin. It is unclear if the sponsor evaluated blood samples for the presence of metabolites other than OH-dalbavancin.
2. The sponsor used a microbiological assay to determine the amount of unchanged drug excreted in feces. Since the microbiological activity of OH-dalbavancin is unknown, the use of a microbiological assay may overestimate the excretion of unchanged dalbavancin in feces.

### 4.3. Pharmacometric Review

#### Pharmacometric Review

NDA number:	21-883
Submission Date:	December 21, 2004
Product:	Dalbavancin for injection (TBD)
Formulation:	Sterile lyophilized powder, (b) (4) 500 mg/vial
Sponsor:	Vicuron Pharmaceuticals, Inc., King of Prussia, PA 19406
Type of Submission:	Original NDA, (NME), Priority review
Primary Reviewer:	Charles R. Bonapace, Pharm.D.
PM Reviewer:	Bruce Green, Ph.D.
Team Leader:	Venkat R. Jarugula, Ph.D.
PM Team Leader:	Joga V. Gobburu, Ph.D.

#### Dalbavancin Population PK covariate analysis

##### Summary:

A population pharmacokinetic analysis of intravenous dalbavancin was performed and included 1,668 dalbavancin plasma concentrations from 532 patients across three Phase 2 (VER001-4 and VER001-5) and Phase 3 (VER001-9) clinical trials. Potential covariates examined with the population PK model included demographics (age, gender, weight, body surface area, and race), creatinine clearance, serum albumin, and concomitant medications and medication groups (presence/absence).

In VER001-4 (n=30), patients with catheter-related blood stream infections were randomized to receive dalbavancin IV 650 mg on day 1 followed by 65 mg daily for up to 13 days (n=8), dalbavancin IV 1000 mg on day 1 and optional 500 mg on day 8 (n=33), or comparator (n=34). Up to seven blood samples were obtained from each patient: Day 1, within 2 hrs prior to and within 2 hrs after the first dose of study medication; Day 4 ( $\pm$  2days); Day 8, within 2 hrs prior to infusion and within 2 hrs post infusion (a single sample could be taken on study Day 8 for those patients who, as per protocol, received only one dose of study drug); EOT ( $\pm$  2 days); and TOC ( $\pm$  2 days).

In VER001-5 (n=34), patients with uncomplicated and complicated skin and skin structure infections were randomized to received dalbavancin IV 1100 mg single dose (n=13), dalbavancin 1000 mg on day 1 followed by 500 mg on day 8 (n=17), or comparator (n=21). For the single dose regimen, plasma samples for dalbavancin concentration determination were collected on study days 8, 10, and 24 whereas patients who received dalbavancin 1000 mg followed by 500 mg on day 8 had plasma samples were collected on study days 8, 20, and 34.

In VER001-9 (n=854), patients with complicated and skin and skin structure infections were randomized to receive dalbavancin IV 1000 mg on day 1 and 500 mg on day 8 (n=571) or comparator (n=283). Blood samples were obtained according to one of two possible schedules. North American sites with odd site numbers used PK schedule #1 initially. Sites with even site numbers began with PK schedule #2. Schedule numbers alternated thereafter with each PK participant. For schedule #1, blood samples were collected at the following times: within 3 hrs of the first dose, within 30 min following the end of the infusion of the first dose, day 4 ( $\pm$  24 hrs), within 24 hrs prior to day 8 infusion, and day 28 ( $\pm$  48 hrs). For schedule #2, blood samples were collected at the following times: within 3 hrs of the first dose, within 24 hrs following the end of the infusion of the first dose, within 30 min after the end of the infusion on day 8, day 14 ( $\pm$  72 hrs), and day 28 ( $\pm$  48 hrs).

During the population PK analysis of dalbavancin, the structural and statistical model supplied by the sponsor was considered to be appropriate to describe the data. Therefore, a covariate analysis was conducted similar to that presented by the sponsor but with assessment of different covariates such as lean body weight, predicted normal weight, and ideal body weight. Refer to the section titled Covariate Analysis for specific formulas.

**Sponsor's Base Model**

(b) (4)



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## 4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics <i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
<b>NDA Number</b>	NDA 21-883	<b>Brand Name</b>	TBD	
<b>OCPB Division (I, II, III)</b>	DPE III, HFD-880	<b>Generic Name</b>	Dalbavancin	
<b>Medical Division</b>	DAIDP, HFD-520	<b>Drug Class</b>	Glycopeptide antibiotic	
<b>OCPB Reviewer</b>	Charles R. Bonapace, Pharm.D.	<b>Indication(s)</b>	Complicated skin and skin structure infections	
<b>OCPB Team Leader</b>	Venkat R. Jarugula, Ph.D.	<b>Dosage Form</b>	Sterile lyophilized powder	
		<b>Dosing Regimen</b>	1000 mg on day 1 followed by 500 mg on day 8	
<b>Date of Submission</b>	December 21, 2004	<b>Route of Administration</b>	Intravenous	
<b>Estimated Due Date of OCPB Review</b>	July 1, 2005	<b>Sponsor</b>	Vicuron Pharmaceuticals, Inc.	
<b>PDUFA Due Date</b>	September 21, 2005	<b>Priority Classification</b>	Priority review	
<b>Division Due Date</b>	September 5, 2005			
<b>1.2.1.1.1.1.1.1 Clin. Pharm. and Biopharm. Information</b>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				Not recommended
Isozyme characterization:	X	5		
Blood/plasma ratio:				
Plasma protein binding:	X			
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<i>Healthy Volunteers-</i>				
single dose:	X	2		VER001-1, VER001-2
multiple dose:	X	2		VER001-1, VER001-2
<b>Patients-</b>				
single dose:				
multiple dose:	X	3		VER001-4, VER001-5, VER001-9
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	2		VER001-1, VER001-2
fasting / non-fasting multiple dose:	X	2		VER001-1, VER001-2
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				Population PK
In-vivo effects of primary drug:				Population PK
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				Population PK
pediatrics:				
geriatrics:				Population PK
renal impairment:	X	3		VER001-3, VER001-11, VER001-13
hepatic impairment:	X	1		VER001-12
Obesity:				
Cardiac repolarization:	X	3		hERG, Purkinje fiber, conscious dog telemetry

Tissue penetration:	<b>X</b>	<b>2</b>		VER01-10, VER001-19
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	<b>X</b>	<b>1</b>		VER001-PK-002
<b>Population Analyses -</b>				
Data rich:				
Data sparse:	<b>X</b>	<b>3</b>		
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>16</b>		
<b>Filability and QBR comments</b>				
	<b>"X" if yes</b>	<b>1.2.1.1.1.1.1.1 Comments</b>		
<b>Application filable?</b>	<b>X</b>			
<b>Comments sent to firm?</b>				
<b>QBR questions (key issues to be considered)</b>	1) What PK/PD data support administration of dalbavancin 1000 mg on day 1 followed by 500 mg on day 8 for cSSSI? 2) How do the pharmacokinetics of dalbavancin in healthy subjects compare to patients with infections? 3) What is the impact of renal impairment on the pharmacokinetics of da bavancin? 4) What is the impact of gender/age on the pharmacokinetics of dalbavancin?			
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>				
<b>Secondary reviewer Signature and Date</b>				

CC: NDA 21-572, HFD-520 (Davi), HFD-880 (Lazor, Selen, Jarugula, Bonapace), CDR (B. Murphy)

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

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Charles Bonapace  
9/20/2005 01:26:28 PM  
BIOPHARMACEUTICS

Vikram Arya  
9/20/2005 02:34:30 PM  
BIOPHARMACEUTICS

Jogarao Gobburu  
9/20/2005 05:43:41 PM  
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Venkateswar Jarugula  
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