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APPLICATION NUMBER:

021883Orig1s000

PHARMACOLOGY REVIEW(S)

Comments on N21883 Dalbavancin
From Abby Jacobs, AD
5/16/14

1. I agree that there are no nonclinical approval issues for this NDA
2. I concur that the appropriate pregnancy category should be C
3. I concur with the reviewer's recommended changes to the labeling

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/s/

ABIGAIL C JACOBS
05/16/2014

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 21883
Supporting document/s: 83
Applicant's letter date: 9/26/2013
CDER stamp date: 9/26/2013
Product: Dalbavancin (b) (4) 500 mg) Injection
Indication: Treatment of Acute Bacterial Skin and Skin
Structure Infection
Applicant: Durata Therapeutics, Inc.
Review Division: Division of Anti-Infective Products
Reviewer: Terry J. Miller, Ph.D.
Supervisor/Team Leader: Wendelyn Schmidt, Ph.D.
Division Director: Sumathi Nambiar, M.D.
Project Manager: Christopher Davi, M.S.

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1 Executive Summary

1.1 Introduction

Dalbavancin powder for injection solution is a second generation, semi-synthetic lipoglycopeptide antibiotic. Glycopeptide antibiotics inhibit the biosynthesis of bacterial cell wall peptidoglycans, a critical target responsible for stabilization of the cell wall and survival of the organism. In vitro and in vivo nonclinical pharmacology and microbiology indicate therapeutic activity for dalbavancin against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). The long terminal elimination half-life ($t_{1/2}$) supports a dosage recommendation of two single doses, administered on Day 1 (1000 mg) and Day 8 (500 mg) of treatment, over a 30 minute infusion period.

Durata Therapeutics, Inc. is pursuing marketing approval for dalbavancin as an intravenous treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of Gram-positive microorganisms. Dalbavancin is not currently approved for another indication. This NDA application was originally submitted to the Agency by Vicuron Pharmaceuticals in 12/2004 and failed to obtain marketing approval for concerns about its efficacy. The current application is the latest resubmission of the NDA application since its withdrawal from the Agency by its previous owner, Pfizer, Inc, in 2008.

The current NDA application contains a large number of in vitro and in vivo pharmacology studies, many in vivo toxicology studies including repeat dose studies with intravenously administered dalbavancin in rats and dogs up to 90 days duration, a full genetic toxicology battery, and several reproductive and developmental toxicity studies in rats and rabbits (Segments 1-3). All of the nonclinical studies conducted with dalbavancin were reviewed prior to the resubmission of the latest application, and with exception of the pivotal juvenile toxicology study, were reviewed by Drs. Kenneth Seethaler and Wendelyn Schmidt. The original NDA application submitted in 12/2004 was found to be approvable by Dr. Wendelyn Schmidt (see DARRTs 8/18/2005). The prior NDA serves as the basis for the pharmacology/toxicology approval decision for the current resubmission, The Applicant has no plans to conduct additional nonclinical studies with dalbavancin and no additional nonclinical studies are recommended at this time.

Clinical investigation of dalbavancin under various Sponsors has generated 21 clinical trials (Phases 1-3) in which human exposure was assessed, with and with out positive and/or placebo controls. As of June 2013, 3442 patients and healthy subjects have been enrolled and received study medication in the dalbavancin clinical development program, at a variety of dose levels, in both single and multiple dose regimens of IV administered dalbavancin.

1.2 Brief Discussion of Nonclinical Findings

Dalbavancin is a lipoglycopeptide which interferes with bacterial cell wall formation and is active against Gram-positive bacteria. Safety pharmacology studies conducted in mice, rats, and rabbits showed no effects on respiration, body temperature, and behavioral or autonomic nervous system parameters; the in vitro hERG channel assay and in vivo studies with telemetered anesthetized and conscious dogs also showed dalbavancin had no significant effects on cardiovascular function. PK properties of dalbavancin were consistent amongst a number of species including humans, with a wide distribution of drug to tissues excluding brain, and a linear response between dose and serum levels. Dalbavancin accumulates in plasma and tissues, and has a very long half-life in both plasma (1-3 week) and tissues: (≥ 6 months). Dalbavancin is minimally metabolized and is excreted very slowly. The cumulative plasma AUC levels from the 28 and 90 day toxicology studies in rats and dogs at which adverse effects are generally observed were 2 to 4-fold and 5 to 7-fold above clinical exposures, respectively. The toxicologic profile of dalbavancin is similar across species; local injection site toxicity, histamine related infusion reactions, and target organ toxicity to the liver and kidney were noted in several species. Histologic correlates including hepatocellular and renal tubular cell necrosis, vacuolation, and degeneration were associated with long lasting, elevated serum LFTs, BUN, and creatinine levels observed with high dose dalbavancin treatment. Dalbavancin is neither a mutagen nor clastogen when tested in a complete genotox battery and is not teratogenic in pregnant rats and rabbits up to maternal toxic doses. The NOAEL for fetal development was 15 mg/kg/day in both species due to similar, delayed ossification of sternebrae and skull noted at higher doses. Changes in the fertility index was observed in male rats and pregnant rat females and peri- postnatal development studies showed a moderate increase (18%) in fetal deaths (2:1) compared to control of unknown cause. There were no other effects on developmental milestones, or on the F1 and F2 generations. Dalbavancin is generally not irritating and the TK and toxicologic profile of dalbavancin in juvenile rats mimics the adults.

1.3 Recommendations

1.3.1 Approvability

From the pharmacology/toxicology perspective, the non-clinical studies conducted with dalbavancin are adequate for approval.

1.3.2 Additional Non Clinical Recommendations

There are no additional non-clinical findings recommendations at this time.

1.3.3 Labeling

Sponsor Suggested labeling: (From Module 1.14 Draft Annotated Labeling of the NDA application submitted in the 9/26/2013 submission)

Note: The human PK values were obtained from healthy volunteers in the hepatic impairment study (Study No. VER001-12) submitted to the NDA. The AUC_{0-∞} value for a 1000 mg dose followed 1 week later by a 500 mg dose was 33851 hr.mg/L or 33.8 mg.hr/mL. Otherwise, where PK values were not available, the highest human dose of 1000 mg was used for comparison (16.7 mg/kg assuming a 60 kg human).

In a resubmission of the NDA application to the Agency in December 2005, former owner Pfizer, Inc. proposed a labeling modification in which 0-24 h AUC values multiplied by 14 days were used in comparing to the human AUC. The Agency agreed to this modification and in a memo to NDA 21883 dated 2/17/2006 in DARRTS, the pharmacology/toxicology reviewer, Dr. Wendelyn Schmidt, presented her interpretation of the modified safety ratios from the animal studies with dalbavancin shown below:

Study	Animal Dose mg/kg/day	Cumulative AUC (sponsor) mg.h/L	Cumulative AUC Reviewer ug.h/mL	Safety ratio Sponsor	Safety ratio reviewer
Seg I rat NOAEL	15	(b) (4)	&	(b) (4)	1.2
Seg I rat adverse effects	45		&		3.5
Seg II rat NOAEL	15		30422 [§]		0.9
Seg II rat adverse effects	30		57134 [§]		1.7
Seg II rabbit NOAEL	15		&		0.7
DX28 rat NOAEL	10		18921		0.6
DX28 rat adverse effects	40		84228		2.5
DX90 rat NOAEL	5		15905		0.5
DX90 rat adverse effects	10		29456		0.9
DX90 dog NOAEL	10		40509		1.2
DX90 dog adverse effects	40		158067		4.7

& used the same numbers as the sponsor.

[§] AUCs were calculated by the reviewer using the least squares method based on plasma levels at 0, 1, 2, 4, 8 and 24 hours.

These agreed to values appear in the pharmacology/toxicology relevant sections of the current labeling.

The Sponsor's proposed labeling and my labeling comments (italics) can be found below:

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category C

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

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

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

8.2 Nursing Mothers

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

(The first sentence of labeling for section 8.1 should include the exposure multiple to the clinical dose for the rabbit embryo-fetal toxicity study. The Sponsor's proposed sentence is modified with the addition of 0.7 (underlined and bolded above) to show the exposure multiple for rabbit is different from rat when comparing the rat to human PK data. Also the sentence regarding the absence of well-controlled studies in pregnant women should be moved to the top of Section 8.1. There are no other recommended changes to the Sponsor's proposed labeling for Sections 8.1 and 8.2").

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

13.2 Animal Toxicology and/or Pharmacology

Increases in serum levels of liver enzymes (ALT, AST), **associated with microscopic findings in the liver** were noted in (b) (4) where dalbavancin was administered daily for 28 to 90 days. **Hepatocellular necrosis was observed in dogs dosed at ≥ 10 (b) (4) for longer than 2 months, i.e., at**

approximately 5 to 7 times the expected human dose on an exposure basis. In addition, renal toxicity characterized by increases in serum BUN and creatinine and microscopic kidney findings was observed in rats and dogs at at (b) (4) doses (b) (4) 5 to 7 times the expected human dose on an exposure basis (b) (4)

(The Division's proposed changes to Section 13.2 "Animal Toxicology and/or Pharmacology" of the Sponsor's labeling are in bold above. The information that should be deleted contains a strikethrough above. Section 13.1 appears fine as written).

2 Drug Information

2.1 Drug

Dalbavancin drug substance is a semi-synthetic cyclic lipoglycopeptide antibiotic comprised of two major families with different structural homology: dalbavancin A and dalbavancin B. The dalbavancin A family, which constitutes (b) (4) of the active drug substance, consists of two subtypes, A₀ and A₁. Dalbavancin B, which constitutes approximately (b) (4) of the active drug substance, is comprised of subtypes B₀, B₁, and B₂.

CAS Registry Number

Dalbavancin A₀: 171500-81-5

Dalbavancin A₁: 171500-90-6

Dalbavancin B₀: 171500-79-1

Dalbavancin B₁: 171500-82-6

Dalbavancin B₂: 871132-03-5

Generic Name

Dalbavancin

Code Name

VER001, BI-397, V-glycopeptide (Vicuron Pharmaceuticals)

PF-03906135 (Pfizer, Inc.)

MDL 63,397 (Marion Merrel Dow)

BI 397 (Biosearch Italia SpA)

DUR001 (Durata Therapeutics, Inc.)

Chemical Name

Dalbavancin A₀: 2-deoxy-1-O-[(3S,15R,18R,34R,35S,38S,48R,50aR)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-D-mannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaaxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-1H,15H,34H-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno[1,14,6,22]dioxadiazacyclooctacosino[4,5-m][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-[(9-methyldecanoyl)amino]-β-Dglucopyranuronic acid

Dalbavancin A₁: 2-deoxy-1-O-[(3S,15R,18R,34R,35S,38S,48R,50aR)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-D-mannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaaxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-1H,15H,34H-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno[1,14,6,22]dioxadiazacyclooctacosino[4,5-m][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-(undecanoylamino)-β-Dglucopyranuronic acid

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

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

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

Molecular Formula/Molecular Weight

Dalbavancin A₀: C₈₇H₉₈N₁₀O₂₈Cl₂ / 1802.7

Dalbavancin A1: C₈₇H₉₈N₁₀O₂₈Cl₂ / 1802.7

Dalbavancin B0: C₈₈H₁₀₀N₁₀O₂₈Cl₂ / 1816.7

Dalbavancin B1: C₈₈H₁₀₀N₁₀O₂₈Cl₂ / 1816.7

Dalbavancin B2: C₈₉H₁₀₂N₁₀O₂₈Cl₂ / 1830.7

Structure or Biochemical Description

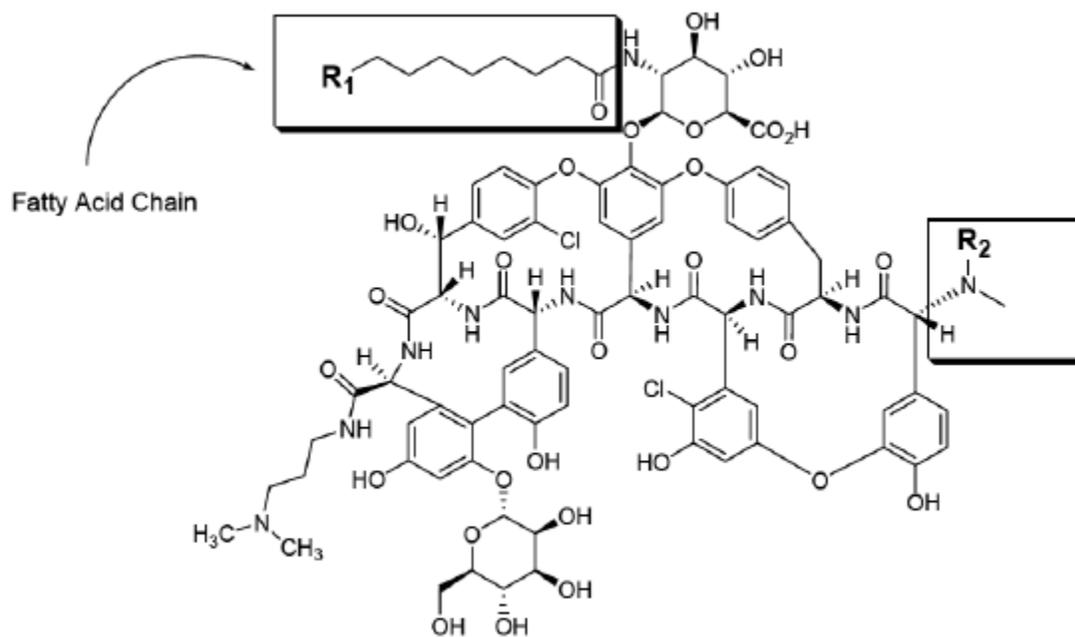


Figure 1. General Structure of Dalbavancin Drug Substance

(Figure 3.2.S.1.2-1 (Structure) in Module 3.2.S (Drug Substance) in the NDA Application)

Table 1. Substitution Pattern for Dalbavancin Homologues

Homologue	R ₁	Number of Carbons R ₁	R ₂
A ₀	CH(CH ₃) ₂	3	H
A ₁	CH ₂ CH ₂ CH ₃	3	H
B ₀	CH ₂ CH(CH ₃) ₂	4	H
B ₁	CH ₂ CH ₂ CH ₂ CH ₃	4	H
B ₂	CH ₂ CH(CH ₃) ₂	4	CH ₃

(Table 3.2.S.1.2-1 (Structure) in Module 3.2.S (Drug Substance) in the NDA Application)

Pharmacologic Class: Lipoglycopeptide Antibiotic

2.2 Relevant INDs, NDAs, BLAs and DMFs: IND 60613

2.3 Drug Formulation

Dalbavancin for injection, 500 mg, is a lyophilized solid, containing dalbavancin hydrochloride equivalent to 500 mg of dalbavancin free base per vial as active ingredient. The dalbavancin IV concentrate solution is prepared by reconstituting the lyophilized solid with sterile water for injection. Prior to dosing, the reconstituted solution must be further diluted in an appropriate intravenous solution. The dalbavancin infusion solution is administered IV. The container closure system consists of a glass vial with a rubber stopper and flip-off seal.

2.4 Comments on Novel Excipients

There are no reported novel excipients in the commercial drug product. A search of the FDA “Inactive Ingredients Search for Approved Drug Products” showed all excipients at concentrations below those found in previously approved intravenous drugs. The quantitative composition of dalbavancin for injection, 500 mg vials are shown in table 2 below.

Table 2. Quantitative Composition of Dalbavancin for Injection, 500 mg vials

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

(b) (4)

^b Anhydrous dalbavancin free base. (b) (4)

2.5 Comments on Impurities/Degradants of Concern

Dalbavancin contains 5 active components (dalbavancin A₀, A₁, B₀, B₁, and B₂) (b) (4)

(b) (4)

(b) (4)

All impurities observed above threshold levels of (b) (4) have been identified and qualified (as per FDA agreement, pre-NDA meeting 10/22/2004) (See Table 3). Drug product impurities detected in dalbavancin can be found on Table 4.

Table 3. Typical Organic Impurities and Specified Drug Substance Components Observed During Development of Dalbavancin at (b) (4)

Peak	Approximate Relative Retention Time (RRT) Range	Description
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(b) (4)

(b) (4)

(Table 3.2.S.3.2-2 in Module 3.2.S (Drug Substance) in the NDA application)

Table 4. Typical Relative Retention Times (RRT) of Drug Product Impurities Observed During Development of Dalbavancin at (b) (4)

Peak	Approximate Relative Retention Time (RRT) Range	Description
(b) (4)		

(Table 3.2.S.3.2-4 in Module 3.2.S (Drug Substance) in the NDA application)

All other organic impurities listed in Section 3.2.S.3.2.2.2 are not routinely observed and are controlled as unspecified impurities in the drug substance (NMT (b) (4))

2.6 Proposed Clinical Population and Dosing Regimen

The recommended dosage regimen for the treatment of ABSSSI caused by susceptible strains of organisms is two IV doses, 1000 mg on Day 1 followed by 500 mg IV on Day 8 (i.e., 14 days of treatment, where the treatment duration for each dose of dalbavancin is defined as 7 days). Each dose of dalbavancin is administered by IV infusion over 30 minutes.

The recommended dosage adjustment for subjects with chronic renal impairment (creatinine clearance < 30 mL/min) and not receiving regular dialysis is 750 mg on Day 1 and 375 mg on Day 8. No dose adjustment is required for subjects with hepatic impairment.

2.7 Regulatory Background

NDA 21883 was initially submitted by Vicuron Pharmaceuticals, Inc. on December 21, 2004, and was withdrawn by Pfizer, Inc. on September 15, 2008. After the submission of IND 60613 and the NDA application in 2004, ownership of dalbavancin changed from Vicuron Therapeutics, to Pfizer Inc., and finally to Durata Therapeutics. Nearly all of the nonclinical studies conducted with the drug product were reviewed as part of the IND or prior to submission of the original NDA application in 2004. A reinstatement request for this NDA application was submitted by Durata Therapeutics to re-establish the active NDA status following a Pre-NDA meeting on April 25, 2012. Dalbavancin received fast track status designation for NDA 21883 on November 7, 2003 for treatment of cSSSI, and Qualified Infectious Disease Product (QIDP) status on October 31, 2012. Durata has requested 5 year NCE exclusivity and has requested a deferral from submitting a

pediatric assessment safety and effectiveness of dalbavancin in children for the initial NDA review.

The proposed proprietary name for the commercial product is “DALVANCE™,” previously submitted to the Agency for review under IND 60,613 on October 24, 2012, and resubmitted on April 25, 2013.

3 Studies Submitted

3.1 Studies Reviewed

Safety Pharmacology:

1. Study 021107.WTD: Effects of Dalbavancin on cloned hERG channels expressed in mammalian Cells. (Reviewed by W. Schmidt)
2. Study 1547/VRS/02: Effects of Dalbavancin on Action Potential Duration (APD) in Rabbit Purkinje Fibers. (Reviewed by W. Schmidt)
3. Study (b) (4) 971102: BI 397: Behavioral Irwin test and effect on body temperature following single intravenous administration in mice. (Reviewed by K. Seethaler)
4. Study (b) (4) 971106: BI 397: Evaluation of effect on the autonomic nervous system following single intravenous administration in conscious rats. (Reviewed by K. Seethaler)
5. Study (b) (4) 981149: BI 397: Evaluation of effect on respiration in the unrestrained conscious rat following single administration by the intravenous route. (Reviewed by K. Seethaler)
6. ABVW-0001: A Cardiovascular safety study of Dalbavancin (VER001) administered to telemetered Beagle dogs. (Reviewed in NDA).
7. Study (b) (4) 971104: BI 397: Evaluation of effect on platelet aggregation induced by collagen and arachidonic acid on rabbit platelets. (Reviewed by K. Seethaler)
8. Study (b) (4) 971103: BI 397: Effect on bleeding time following single intravenous administration in the rat. (Reviewed by K. Seethaler)
9. Study (b) (4) 981150: BI 397: Evaluation of hemodynamic effects following intravenous dosing in the anaesthetized dog. (Reviewed by K. Seethaler)
10. Study (b) (4) 990417: BI 397: Evaluation of hemodynamic effects following intravenous dosing in the anaesthetized dog. (Reviewed by K. Seethaler).
11. Study (b) (4) 990481: Action of noradrenaline on hypotensive effects of BI 397 (batch 011) in anaesthetized dogs. (Reviewed by K. Seethaler).

Pharmacokinetics - (All summarized in the NDA reviewed by W. Schmidt):

1. Study GE028-03: Dalbavancin uptake in mouse macrophage cell line (5774).
2. Report (b) (4) -116D-0301B: Distribution of ¹⁴C-Dalbavancin in rat livers by autoradioluminography and microradiography.
3. Study (b) (4) 980208: [³H]-BI 397. Whole-body autoradiography study in the rat after single intravenous administration.
4. Study (b) (4) 012140: A study of quantitative tissue distribution and bile excretion following single continuous intravenous infusion of ³H Dalbavancin in male rats.

5. Report (b) (4)-116D-0301: Distribution of ¹⁴C-Dalbavancin in dog livers by autoradioluminography and microradiography.
6. ABVZ-0002: Dermal uptakes of ¹⁴C-Dalbavancin following intravenous administration to (b) (4) minipigs.
7. Wise 2000: Report on in vitro studies on BI397 conducted at (b) (4)
8. GE058-04: Protein binding of MAG and OH-Dalbavancin.
9. GE023-04: Pharmacokinetic of Dalbavancin in mouse pilot IV study.
10. GE063-04: Pharmacokinetic of Dalbavancin in mouse pilot IP study.
11. Study GE027-99: BI 397 Pharmacokinetics in the rat.
12. Study GE035-99: BI 397 Pharmacokinetics in the rabbit.
13. Study (b) (4) 971101: BI 397: Pharmacokinetics study after a single intravenous administration in the dog.
14. Report 01098-XBL03135: Mass balance and metabolism of ¹⁴C-Dalbavancin following a single IV infusion of 20 mg/kg to male rats.
15. XBL03131-RPT01096: Mass balance of ¹⁴C-Dalbavancin following a single IV dose of 20mg/kg to the dog.
16. RPT01059-XBL03817: In vivo study of Dalbavancin as inducer of rat Cytochrome P450 enzymes.
17. Study GE047-01: Pharmacokinetics and excretion of Dalbavancin in the rat.
18. (b) (4) Study-XBL012139: VER001: A mass balance study following a continuous intravenous infusion of ³H-VER001 in male rats. (Reviewed with serial # 065/074, W. Schmidt)
19. Study XBL03135-RPT01058: mass balance and metabolism of ¹⁴C-Dalbavancin following a single IV infusion of 20 mg/kg to male rats.
20. XBL03131-RPT01038: mass balance of ¹⁴C-Dalbavancin following a single IV dose of 20mg/kg to the dog.

General Toxicology:

1. Study (b) (4) 971094: Single dose toxicity study in mice treated with the test article BI 97 by oral and intravenous routes. (Reviewed by K. Seethaler)
2. Study (b) (4) 971093: Single dose toxicity study in rats treated with the test article BI 397 by oral and intravenous routes. (Reviewed by K. Seethaler)
3. Study (b) (4) 971095: Dose range-finding study in Sprague Dawley CrI:CD (SD) BR rats treated with the test article BI 397 administered by intravenous route at the doses of 0, 25, 75 and 150 mg/kg/day for two consecutive weeks. (Reviewed by K. Seethaler, W. Schmidt)
4. Study (b) (4) 971096: 4-week intravenous toxicity study in Sprague Dawley CrI:CD (SD) BR rats treated with the test article BI 397 administered by intravenous route at the doses of 0, 5, 10, 20 and 40 mg/kg/day followed by 4 weeks of recovery. (Reviewed by K. Seethaler, W. Schmidt)
5. Study (b) (4) 980831: 4-week repeated dose toxicity study in Sprague Dawley CrI:CD (SD) BR rats treated with the test article BI 397 administered by intravenous route at the doses of 0, 10, 20, 40 and 80 mg/kg/day followed by 4 weeks of recovery. (Reviewed by K. Seethaler, W. Schmidt)

6. Study (b) (4) 990942: BI397: Pilot study in no-pregnant female rabbits by intravenous route (Reviewed by K. Seethaler, W. Schmidt)
7. Study (b) (4) 971097: Dose range-finding study in Beagle dogs treated with the test article BI 397 administered by intravenous route. (Reviewed by K. Seethaler, W. Schmidt)
8. Study (b) (4) 990975: 2-week toxicity study in Beagle dogs treated with the test article BI 397 administered by intravenous at the doses of 0 and 10 mg/kg/day (Reviewed by K. Seethaler, W. Schmidt).
9. Study (b) (4) 971098: 4-week repeated dose toxicity study in Beagle dogs treated with the test article BI 397 administered by intravenous route at the doses of 0, 5, 10, 20 and 40 mg/kg/day, followed by 4 weeks of recovery at the dose of 20 mg/kg/day. (Reviewed by K. Seethaler, W. Schmidt)
10. Study (b) (4) 980779: 4-week repeated dose toxicity study in Beagle dogs treated with the test article BI 397 administered by intravenous route at the doses of 0, 10, 20 and 40 mg/kg/day, followed by 4 weeks of recovery at the dose of 40 mg/kg/day, with additional group of animals treated at 60 mg/kg/day. (Reviewed by K. Seethaler, W. Schmidt)
11. Study 168-002: A three month subchronic toxicity study with Dalbavancin (VER001) in Sprague Dawley rats. (Reviewed by W. Schmidt)
12. Study 168-003: A three month subchronic toxicity study with Dalbavancin (VER001) administered via intravenous injection to Beagle dogs. (Reviewed by W. Schmidt).

Genetic Toxicology (Reviewed by K. Seethaler):

1. Study (b) (4) 971099: Study of the capacity of the test article BI 397 to induce gene mutation in v79 Chinese hamster lung cells.
2. Study (b) (4) 980514: Study of the capacity of the test article BI 397 to induce chromosome aberrations in Chinese hamster ovary cells (CHO).
3. Study (b) (4) 990751: Micronucleus induction in bone marrow cells of mice treated by intravenous route with the test article BI 397.

Reproductive Toxicology (Reviewed by W. Schmidt):

1. Study (b) (4) 10430: Fertility and early embryonic development by intravenous route in rats.
2. Study (b) (4) 990790: Preliminary embryo-fetal development study in Crl:CD (SD) BR rats of the test article BI 397 administered by intravenous route at the dosages of 0, 5, 15, 45 mg/kg/day.
3. Study (b) (4) 990752: Preliminary embryo-fetal development study in New Zealand white rabbits of the test article BI 397 administered by intravenous route at the dosages of 0, 7.5, 15, 30 mg/kg/day.
4. Study (b) (4) 09070: BI 397 embryo-fetal development study in rats by intravenous route.
5. Study (b) (4) 09080: embryo-fetal development study in rabbits by intravenous route.
6. Study 622-002: Intravenous developmental and peri-/postnatal reproduction toxicity study of Dalbavancin (VER 001) in rats, including a postnatal behavioral/functional evaluation. (Reviewed with NDA)

Special Toxicology Studies

1. Study 622-010: Intravenous repeated dose 28-day immunotoxicity study of Dalbavancin (VER001) in rats. (Reviewed by W. Schmidt).
2. Study (b) (4) 980119: Skin sensitization test in guinea-pigs treated with the test article BI 397. (Reviewed by K. Seethaler).
3. Study (b) (4) 980117: Acute dermal irritation study in New Zealand White rabbits treated with the test article BI 397/011. (Reviewed by K. Seethaler).
4. Study (b) (4) 980118: Acute eye irritation study in New Zealand White rabbits treated with the test article BI 397/011. (Reviewed by K. Seethaler).
5. Study LIA00402: Intravenous repeated-dose toxicity study of dalbavancin in juvenile rats (Reviewed by T. Miller)

(Reviewer's comment: Nearly all of the nonclinical studies were submitted to IND 60613 and/or NDA 21883 and were reviewed by Drs. Seethaler and Schmidt prior to, or during the NDA application review in 2004. I reviewed the pivotal juvenile toxicity study in rats with dalbavancin submitted to IND 60613 on 5/2013).

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- IND 60613 (Original IND Review, Pharmacology/Toxicology Review by Dr. Kenneth Seethaler, (in DARRTS 8/2001))
- IND 60613 (IND Review, Pharmacology/Toxicology Reviews by Dr. Wendelyn Schmidt (in DARRTS 3/2003, 4/2003, 10/2003, 3/2005, 7/2005))
- IND 60613 (IND Review, Pharmacology/Toxicology Review by Dr. Terry Miller (in DARRTS 10/2012, 6/2013))
- NDA 21883 (Original Submission 12/2004), Pharmacology/Toxicology Review by Dr. Wendelyn Schmidt (in DARRTS 8/18/2005))
- NDA 21883 (Resubmission 12/2005), Pharmacology/Toxicology Review by Dr. Wendelyn Schmidt (in DARRTS 2/24/2006))

(Reviewer's comment: The next sections contain key findings of the pharmacology and toxicology of dalbavancin as observed in a large number of in vitro and in vivo nonclinical studies conducted in several species with the drug product. For a more comprehensive review of the results from each of the studies, please refer to the above referenced reviews, particularly the NDA application review by Dr. Wendelyn Schmidt completed in 2005).

4 Pharmacology

4.1 Primary Pharmacology

The pharmacology of dalbavancin was originally reviewed by the microbiologist review team, particularly Dr. Fred Marsik (2004). Dalbavancin is a lipoglycopeptide antibiotic

that interferes with cell wall formation and is active against Gram-positive bacteria, including strains resistant to other antibacterials, including methicillin-resistant *Staphylococcus aureus* (MRSA). Primary pharmacodynamic studies include mechanism of bacterial action, in vitro activity against bacterial isolates, and activity in animal models of infection.

4.2 Secondary Pharmacology

- Dalbavancin showed minimal to no binding affinity to any targets in a panel of 120 isolated receptors, ion channels, uptake sites, and enzymes at a concentration of 100 uM.

4.3 Safety Pharmacology

- Dalbavancin had no effect on respiration; body temperature; behavioral (Irwin) and autonomic nervous system parameters; and bleeding times at doses administered up to 20 mg/kg IV in mice and rats.
- No effects on platelet aggregation were noted in rabbit platelets (in vitro) at concentrations of dalbavancin up to 1 mM.
- Dalbavancin had negligible effects on ether-a-go-go (hERG) channels at the maximum feasible dose, however this dose was approximately 1/10th of plasma levels seen clinically (180 ug/mL).
- Four studies in conscious and anesthetized, telemetered dogs showed a single high dose of 60 mg/kg intravenous dalbavancin had no effect on blood pressure, heart rate, or QTc interval; no electrocardiograph arrhythmias, conduction disturbances, or qualitative abnormalities were observed.
- All safety pharmacology studies appear to have been performed adequately, with a positive control group included in the mouse, rat, rabbit, and hERG studies.
- The overall conclusion of the safety pharmacology studies is that dalbavancin does not affect cardiac conduction or circulatory parameters.

5 Pharmacokinetics/ADME/Toxicokinetics

- Dalbavancin has a long plasma (1-3 weeks) and tissue half-life (≥ 6 months) and persists in the liver and kidneys of animals for extended periods.
- Dalbavancin distributes widely to tissues, with no significant fat localization and minimal penetration of the CNS.
- No gender differences were noted for any PK parameters after single and multiple dose treatment of dalbavancin in rats and dogs; AUC values were dose-proportional and were similar across studies and across species.
- Dalbavancin accumulated after the first 28 days of repeat dosing in rat and dogs, with a 2-fold greater plasma level observed on Day 28 compared to the first day in both species; however no further accumulation was noted between Days 28 and 90 post-dose.
- Minimal to moderate metabolism was noted for dalbavancin in rat and dog, with nearly 72% of the major metabolites (mannosyl aglycone dalbavancin (MAG) and hydroxyl dalbavancin (OH-dalbavancin)) and 87-89% of parent dalbavancin bound to serum proteins.

- However, dalbavancin was not generally metabolized by human liver and kidney microsomes and neither induced nor inhibited their P450 metabolic activity in vitro.
- Excretion of dalbavancin occurred over a long period of time with a greater percentage of parent radioactivity detected in urine compared to feces; extensive retention of accumulated drug (> 12% of total dose) was detected in tissues in dogs 181 days after a single dose treatment.
- The pharmacokinetic/toxicokinetic parameters for single and repeat doses of dalbavancin administered to mice and dogs are in tables 5 and 6 below.

Table 5. Species Comparison of the Pharmacokinetic Parameters of a Single IV Dose of Dalbavancin

Pharmacokinetic parameters with single intravenous doses of Dalbavancin									
Ref #	Species	N	Sex	Dose mg/kg	Analysis method	Time course	Cmax mg/L	AUC mg.hr/L	T _{1/2} h
9	ICR mouse	3	F	5	Micro	0.08-144 h	53 ± 2	200	---
				20	Micro		241 ± 13	1071	62
10	ICR mouse	3	F	5*	Micro	0.08-144 h	15	176	---
				20*	Micro		71	848	53
11	SD rat	5	M	20	Micro	0.05-144 h	333 ± 32	2745 ± 441	14 ± 1
17	SD rat	3	M	20	LC/MS/MS	0.08-248 h	323	3067	124
4	SD rat	3	M	20	³ H	0.08-1680 h	53.4	2180	321
12	NZW rabbit	5	M	20	Micro	0.05-72 h	372 ± 43	2231 ± 196	14 ± 1
13	Beagle dog	3	M	5	HPLC	0.08-120 h	51 ± 5	1030 ± 93	25 ± 5
			F				82 ± 9	1356 ± 107	25 ± 5
19	Beagle dog (b)(4)	4	M	20	¹⁴ C	0-181 d	233 ± 20	6515 ± 405	646 ± 96
1	mini-pig	1	F	10	¹⁴ C	0.25-648	109 ± 16	3696 ± 319	91 ± 18

*intraperitoneal dosing; --- indicates parameter not calculated

(Table 4 appears on Page 13 of the original NDA application review by Dr. Wendelyn Schmidt)

Table 6. Species Comparison of the Toxicokinetic Parameters of Daily, Repeat IV Dosing with Dalbavancin

Toxicokinetics of Dalbavancin in rats and dogs								
Species	Schedule	Dose mg/kg	Day	Males		Females		
				Cmax ug/mL	AUC ug.h/mL	Cmax ug/mL	AUC ug.h/mL	
SD rat	DX28d N=2/time-point	5	1	---	280	36	429	
			23	41	528	62	642	
		10	1	70	1056 ^a /787 ^b	78	731/1062	
			23	94	1258/1300	124	1431/1417	
		20	1	142	1631/1853	140	1213/2308	
			23	236	3293/3756	194	2648/4001	
		40	1	248	2688/4134	216	2260/4616	
			23	366	5403/7837	472	4082/6743	
		80	1		----/8830		---- /8204	
			23		---/15220		----/11366	
		DX90d N=1/time point	5	28	105	1041	89	895
				90	112	1173	97	1100
	10		28	231	1839	196	1759	
			90	171	2159	155	2049	
	40		28	548	4837	511	5477	
			90	---	---	---	---	
Beagle dog	DX28 N=1/time point	5	1	40	464	66	690	
			28	45	664	79	993	
		10	1	96 ^c /114 ^d	1086/1541	92/100	1135/1344	
			28	123/141	1576/2455	114/137	1647/2019	
		20	1	223/280	2782/3735	200/172	2744/2686	
			28	240/505	4323/5592	292/444	4423/4702	
		40	1	506/538	5073/6836	478/598	5188/6334	
			28	547/900	6491/13004	544/576	7336/13201	
		60	1	---/991	---/11749	---/858	---/10733	
			28	---/1190	---/14737	---/987	---/13286	
		DX90d N=4	5	1	82	673	81	630
				28	118	1342	122	1424
	90			108	1238	102	1110	
	10		1	151	1351	159	1354	
			28	257	3182	221	2582	
			90	237	3193	207	2594	
	40	1	608	5448	667	6168		
		28	875	11719	834	11714		
90		733	10573	895	12008			

^aStudy # (b) (4) 971096, ^bStudy # (b) (4) 980831, ^cStudy #: (b) (4) 971098, ^dStudy #: (b) (4) 980779
(Table 5 appears on Page 14 of the original NDA application review by Dr. Wendelyn Schmidt)

6 General Toxicology

- Dalbavancin toxicity and toxicokinetics were evaluated after a single dose in mice and rats; after repeated intravenous doses administered daily to rats for 14, 28, and 90 days; and to dogs for 28 and 90 days.
- Dalbavancin caused dose (> 30 mg/kg) and infusion rate (< 11 minutes) dependent infusion reactions (facial, paw, skin swelling and redness; mucosal pallor, salivation, vomiting, sedation, and increased heart rate) in dogs attributed to transient histamine release.
- Local injection site toxicity in the tails of rats with repeat dosing was dose limiting and often led to early termination.
- Liver and kidney were the primary targets for dalbavancin toxicity; high doses of dalbavancin caused elevated serum LFTs, BUN, and creatinine levels, associated with hepatocellular and renal tubular necrosis, vacuolation, and degeneration.
- Serum LFTs and renal proteins remained elevated for months after dosing had stopped in dogs; likely due to the persistence of dalbavancin in the target organs.
- Cytoplasmic vacuoles and dark pigments observed in macrophages and other cell types (e.g. hepatocytes, renal tubular epithelium, and pancreatic acinar epithelium) in multiple organs in treated rats and dogs were of unknown toxicologic consequence.
- The nonclinical intravenous studies conducted with dalbavancin in rats and dogs, and associated target organs, AUC at the No-Observed-Adverse-Effect-Level (NOAEL) and AUC at the lowest toxic level are included in Table 7 below.

Table 7. Nonclinical Intravenous Studies Conducted Dalbavancin

Intravenous studies conducted with dalbavancin						
Species	Schedule	Doses mg/kg	Target organs	LD or NOAEL mg/kg	AUC* at NOAEL ug.h/mL	AUC at Lowest Toxic level
CD-1 Mouse	1X	160, 200, 250	CNS	LD50= 200	---	---
SD rat	1X	93, 102, 112	CNS	LD10 =93	---	---
SD rat	DX14	25, 75, 150	Liver	NOAEL= 25 LLD = 25		
SD rat	DX 28	10, 20, 40, 80	Liver, kidney, Injection site	NOAEL= 10	D1 = 909 D23= 1351	D1 = 1751 D23 = 3424
SD rat	DX 90	5, 10, 40	Liver, kidney injection site, pancreas	NOAEL< 5	D28 = 968 D90= 1136	D28 = 1799 D90=2104
Beagle dog	DX28	5, 10, 20, 40, 60	Liver, kidney, injection site	NOAEL = 10	D1 =1442 D28 = 2237	D1 = 3210 D28= 5147
Beagle dog	DX90	5, 10, 40	Liver, kidney, injection site	NOAEL = 5	D1 = 651 D90 = 1174	D1= 1352 D90= 2893

--- no values collected, *AUC values are mean of male and female combined (no significant gender differences notes)

(Table on page 17 of the original NDA application review by Dr. Wendelyn Schmidt).

7 Genetic Toxicology

- The GLP genetic toxicology studies conducted with dalbavancin (VER001) included the following assays:
 1. Gene Mutation Assay at HGPRT Locus in V79 Chinese Hamster Lung cell line (in vitro)
 - Dalbavancin did not increase mutation frequencies.
 2. Chromosome Aberration Assay in Chinese Hamster Ovary cells (in vitro)
 - Dalbavancin did not induce chromosome abnormalities.
 3. Micronucleus Assay in Mouse Bone Marrow (in vivo)
 - Dalbavancin did not change the ratio of normochromatic to polychromatic erythrocytes, and did not increase micronucleus frequency.

- The findings from the in vitro and in vivo genetic toxicology studies indicate dalbavancin (VER001) is neither mutagenic nor clastogenic.
- All assays appeared to have been conducted appropriately and positive and negative controls yielded expected results.

8 Carcinogenicity

- No carcinogenicity studies were conducted with dalbavancin and were not considered necessary as this drug is indicated for short term use.

9 Reproductive and Developmental Toxicology

- The reproductive toxicology battery with dalbavancin included fertility, embryo-fetal development, and peri- and post-natal development studies in rats and rabbits; all studies appear to have been conducted adequately.
- Fertility studies with dalbavancin in rats showed a decreased fertility index at 45 mg/kg/day (the maximum dose tested) with correlative glandular atrophy in the prostate and seminal vesicles and decreased secretory material in males, and increased resorptions in pregnant females; the NOEL for mating and fertility was 15 mg/kg/day.
- Dalbavancin was not teratogenic in rats and rabbits at doses up to the maternal toxic dose in rabbits (15 mg/kg/day) and up to the maternal NOAEL and maximum dose tested in rat (45 mg/kg/day).
- There was no effect on fetal or maternal body weights with dalbavancin treatment up to the maternal toxic dose; the NOAEL for fetal development was 15 mg/kg in both species due to delayed ossification of sternbrae and skull at 45 mg/kg/day.
- Prenatal and postnatal development (Segment III) studies in rats with dalbavancin showed a significant number of deaths (18.7%) in the high dose treatment group, despite minimal maternal toxicity, with nearly twice as many pup deaths in the high dose group compared to control.
- No significant, treatment related differences in developmental parameters, mating index, and number of implantation sites were noted; the NOAEL values for the F0, F1, and F2 generations were 30 mg/kg, 15 mg/kg, and 15 mg/kg, respectively.
- Plasma levels of dalbavancin in the pups was approximately 1/10th that in the dams and parent drug was detected in secreted mother's milk at levels 1/10th that of maternal plasma levels).

10 Special Toxicology Studies

- Dalbavancin (VER001) was not deemed to be irritating to eyes or intact skin of rabbits and was classified as a non-irritant.
- No sensitization was detected in a typical guinea pig skin sensitization study with repeat dermal challenge with dalbavancin (VER001).
- Dalbavancin had minimal biologic effect on the innate- and/or cell-mediated immunity of rats after 28 days of IV treatment.

- Dalbavancin was generally well tolerated by juvenile rats, with a similar toxicokinetic profile and similar organ targets of toxicity (liver & kidney) as adult animals; exposure values limited by infusion site toxicity were 10-30 fold less in juvenile animals than observed clinically.

11 Integrated Summary and Safety Evaluation

Dalbavancin is a lipoglycopeptide which interferes with bacterial cell wall formation and is active against Gram-positive bacteria. Safety pharmacology studies conducted in mice, rats, and rabbits up to 20 mg/kg showed no effect on respiration, body temperature, behavioral (Irwin) and autonomic nervous system parameters. Variable changes in blood pressure were noted in some studies with several dogs at 60 mg/kg suggesting a possible dose-related histaminic response to dalbavancin. In addition, dalbavancin showed no significant effect on any measured cardiac or circulatory parameters in vitro and in vivo in dogs. This included, negative findings in the hERG channel assay (at 1/10th the observed clinical plasma levels) and no drug related changes in any measured cardiovascular assessments (i.e. blood pressure, heart rate, QTC interval, arrhythmias, cardiac electrical conduction) in at least 4 cardiovascular studies with telemetered dogs at 40 to 60 mg/kg.

The pharmacokinetic properties of dalbavancin were examined in a variety of species, including rats, dogs, and humans. Intravenously administered dalbavancin distributes widely to tissues, but is generally excluded from the CNS by the blood brain barrier. No gender specific effects were noted and C_{max} and AUC levels generally increased linearly with dose across species. Dalbavancin accumulated 2-fold with repeat daily dosing in rats and dogs up to 28 days, with minimal additional accumulation noted between Days 28 and 90. Dalbavancin is minimally metabolized in animals and in vitro in human liver and kidney microsomes. The half-life of dalbavancin was determined to be quite long; 1-3 weeks in the plasma and ≥ 6 months in the tissues. Excretion of dalbavancin was slow, with parent detected in both urine and feces. Dalbavancin neither inhibits nor induces P450 metabolic activity in vitro. The AUC at the NOAEL dose in rats and rabbits at 28 and 90 days of dosing ranged between 1100 and 2300 ug*h/mL and the adverse effects are noted to occur at an AUC range between 2000 and 5200 ug*h/mL. The human AUC exposure value in healthy volunteers from two doses, 1000 mg on Day 1 and 500 mg on Day 8, was 33815 ug*h/mL. The human exposure at the proposed 2 dose regimen is nearly 15-30-fold greater than the NOAEL doses in rats and dogs, and 6-15 fold greater than the lowest toxic levels in the animals.

In prior discussions in 2006 between Dr. Schmidt and Pfizer Inc. (the former owner of dalbavancin), an agreement was reached to allow use of a cumulative AUC value (AUC_{cum}) or (AUC_{0-24h} x 14 days) to better reflect the shorter half-life of dalbavancin in animals compared to humans, and to perhaps provide a better assessment of AUC relative to the limited 2-dose regimen proposed in the clinic (Table 8; from Dr. Schmidt's memo to the Division file for NDA 21883 in DARRTS 2/26/2006).

Table 8. Animal:Human Safety Ratios from Cumulative AUC_{0-24h} Values In Healthy Volunteers (Trial No. VER001-12) and Animal Toxicology Studies (Schmidt, 2/26/2006)

Study	Animal Dose mg/kg/day	Cumulative AUC (sponsor) mg.h/L	Cumulative AUC Reviewer ug.h/mL	Safety ratio Sponsor	Safety ratio reviewer
Seg I rat NOAEL	15	(b) (4)	&	(b) (4)	1.2
Seg I rat adverse effects	45		&		3.5
Seg II rat NOAEL	15		30422 ^{\$}		0.9
Seg II rat adverse effects	30		57134 ^{\$}		1.7
Seg II rabbit NOAEL	15		&		0.7
DX28 rat NOAEL	10		18921		0.6
DX28 rat adverse effects	40		84228		2.5
DX90 rat NOAEL	5		15905		0.5
DX90 rat adverse effects	10		29456		0.9
DX90 dog NOAEL	10		40509		1.2
DX90 dog adverse effects	40		158067		4.7

& used the same numbers as the sponsor.

^{\$} AUCs were calculated by the reviewer using the least squares method based on plasma levels at 0, 1, 2, 4, 8 and 24 hours.

(Table 8; from Dr. Schmidt's memo to the Division file for NDA 21883 in DARRTS 2/26/2006).

In the latest NDA application, Durata submitted Table 3 in **Module 2.4 Nonclinical Overview** (pg 26) comparing similar cumulative animal and human AUC exposure ratios from nonclinical studies and their choice of the PK clinical trial (VER-001-PK) (Table 9).

Table 9. Animal and Human Exposures and Exposure Ratios (Sponsor)

Animal Parameter	Animal AUC _{cum} ^a	Animal : Human Exposure Ratios	
		AUC _{cum} /AUC _{0-inf} Ratio ^b	Dose (mg/kg/day) Ratio ^c
(b) (4)			

The Applicant's table of AUC comparisons appeared slightly different from Dr. Schmidt's table in DARRTS (2/26/2006). To address these differences, I reexamined the cumulative AUC values in the 28 and 90 day toxicology studies in rats and dogs, and compared these values to AUC values from the Applicant's preferred PK trial (VER001-PK-001) **and** the reviewer's preferred trial for PK comparison (VER001-12). Please note that there were several differences between the Tables 8 and 9 including the following: (

(b) (4)

My revised comparison of the cumulative AUC values in animals to human PK results from both trials (VER001-PK-001 and VER001-12) can be found in Table 10 below. In most cases, the Applicants safety margins calculated from either clinical trial are greater than determined in my own assessments, apparently due to differences in the cumulative animal AUC values. Although its not clear which AUC values the Applicant used in their original calculation, the use of cumulative AUC values generated safety margins in the range of 2 to 4 and 5 to 7-fold in rats and dogs, respectively, above the clinical exposures in the 28 and 90 day toxicology studies. Because the individual TK values in animals showed significant variability, some caution should be used in interpreting these safety margins as true margins in a risk assessment with dalbavancin. The most important message is that repeated dosing with dalbavancin results in a significant and long-lasting accumulation in tissues with very slow clearance and tissue retention ≥ 6 months in animals.

Table 10. Comparison of the AUC Exposure Values in 28 and 90 Day Toxicology Studies in Rats and Dogs to Clinical Trials (VER001-PK-001 and VER001-12)

Study	Animal AUC _{0-24h} (ug*h/mL) last day	Animal AUC _{cum} (ug*h/mL) (Sponsor)	Animal AUC _{cum} (ug*h/mL) (Reviewer)	Animal:Human Exposure Ratios			
				AUC _{cum} ratio (Sponsor) HuAUC = 26000 ug*h/mL	AUC _{cum} ratio (Sponsor) HuAUC = 33851 ug*h/mL	AUC _{cum} ratio (Reviewer) HuAUC = 26000 ug*h/mL	AUC _{cum} ratio (Reviewer) HuAUC = 33851 ug*h/mL
NOAEL DOSE							
28 day dalbavancin							
Rat (10 mg/kg)	1351	50000	18914	2	1.5	0.7	0.6
Dog (10 mg/kg)	2237	80000	31318	3	2.4	1.2	0.9
90 day dalbavancin							
Rat (5 mg/kg)	1136	102000	15904	4	3.0	0.6	0.5
Dog (5 mg/kg)	1174	105000	16436	4	3.1	0.6	0.5
ADVERSE EFFECTS							
28 day dalbavancin							
Rat (40 mg/kg)	5903	144000	82642	6	4.3	3.2	2.4
Dog (40 mg/kg)	10007	328000	140098	13	9.7	5.4	4.1
90 day dalbavancin							
Rat (40 mg/kg)	5157	189000	72198	7	5.6	2.8	2.1
Dog (40 mg/kg)	11290	260000	158060	10	7.7	6.1	4.7

Cumulative area under the curve (AUC_{cum}) measurements are AUC_{0-24h} values at end of dosing x 14 days

Clinical Trial No VER001-PK-001: Mean AUC = 26000 ug*h/mL

Clinical Trial No VER001-12: Mean AUC = 33851 ug*h/mL

The Applicant compared animal TK data to human PK results from Clinical Trial No. VER001-PK-001.

The Reviewer compared animal TK data to human PK results from Clinical Trial No. VER001-12.

The toxicologic profile of dalbavancin appears similar across species. Local injection site toxicity appeared to be the dose-limiting toxicity, with evidence of dose and infusion time dependent infusion reactions (skin swelling and redness; salivation; vomiting, sedation, and increased heart rate) in dogs likely attributed to histamine release. Liver and kidney were there primary target organs for dalbavancin toxicity; high doses of

dalbavancin caused elevated serum LFTs (primarily ALT and AST), BUN, and creatinine levels, associated with microscopic changes including hepatocellular and renal tubular cell necrosis, vacuolation, and degeneration. Interestingly, serum LFTs and renal protein markers remained elevated in rats and dogs for up to 15 months after dosing was terminated, indicating continued injury with persistence of dalbavancin in the tissues. Iron-negative, cytoplasmic vacuoles and dark pigments observed in macrophages and other cell types (i.e. hepatocytes, renal tubular epithelium, and pancreatic acinar epithelium) were visible in multiple tissues of unknown consequence. Similarly, pancreatic acinar vacuolation/degeneration/apoptosis noted in greater frequency of the rat were considered toxicologically insignificant. Increased dosing frequency between 28 and 90 days in rats and dogs appeared only to affect the severity of finding; no new toxicities were noted with increased duration of dosing.

Both the genetic toxicology and reproductive and developmental toxicology battery (Segments 1-3) of studies were considered adequate. Dalbavancin was neither mutagenic or clastogenic in the AMES and mammalian chromosome aberration assays, as well as in the rat in vivo bone micronucleus assay. Dalbavancin is also not teratogenic. No terata were observed in pregnant rabbits and pregnant rats dosed up to the maternal toxic dose in rabbits (15 mg/kg/day) or at the maximum feasible dose in rats (45 mg/kg/day). Pregnant rabbits often show gastrointestinal disturbance with antimicrobial treatment that can manifest into maternal malnutrition, body weight loss, and various immunological changes; often associated with increased resorptions, spontaneous abortions, decreased fetal weights, and embryo-fetal effects. No maternal or fetal body weight changes were noted in either pregnant species up to the maternal toxic (rabbit) or maximum feasible dose (rats); the NOAEL for fetal development was 15 mg/kg/day in both species due to delayed ossification of sternbrae and skull noted at higher doses. A decreased fertility index was observed with dalbavancin administered at 45 mg/kg/day in rats with glandular atrophy in the prostate and seminal vesicles of males, and increased resorptions in pregnant females. Prenatal and postnatal development studies in rats showed a significant number of deaths (18.7%) in the high dose group of unknown cause, despite minimal maternal toxicity, with nearly twice as many pup deaths compared to control. There were no other effects on developmental milestones, or on the F1 and F2 generations. Dalbavancin readily distributes to breast milk at 1/10th the plasma levels observed in rats.

Dalbavancin is not irritating to the skin or eyes of animals. Juvenile toxicity studies with dalbavancin in rats showed similar PK parameters and targets of organ toxicity (namely liver and kidney) as adult animals limited by local infusion site toxicity; exposures in juvenile animals were similarly 10-30 fold less than observed clinically.

Recommendations: From the pharmacology/toxicology perspective, dalbavancin (NDA 21883) is approvable.

12 Appendix/Attachments

None.

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/s/

TERRY J MILLER
03/10/2014

WENDELYN J SCHMIDT
03/10/2014

I concur with Dr. Miller's assessment of the thoroughness and interpretation of submitted data for this NDA.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21883 Applicant: Durata Therapeutics, Inc. Stamp Date: 9/26/2013

Drug Name: Dalbavancin NDA/BLA Type: 505(b)(1)
(b) (4) **500mg Injection**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The PharmTox review written by Dr. Wendelyn Schmidt for the initial NDA submission in 12/2004 will serve as the basis for my review of the NDA resubmission. Since that time, the Sponsor has completed a single juvenile toxicology study with Dalbavancin which has been evaluated and will be included in my review.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		See Comment to Question #1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		The current formulation appears to be similar to the drug formulation described in the original NDA application submitted 12/2004.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		See Comment to Question #1.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		See Comment to Question #1.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	X		The proposed drug has no specific abuse potential.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None identified.

Terry J. Miller, Ph.D. 9/26/2013

 Reviewing Pharmacologist Date

Wendelyn Schmidt, Ph.D. 9/26/2013

 Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

TERRY J MILLER
10/30/2013

WENDELYN J SCHMIDT
10/30/2013

Memo to the Division File

NDA Number: 21-883

Compound: Dalbavancin

Serial Number of Submission: Resubmission, December 2005

From: Wendelyn Schmidt

Through: Terry Peters, Team Leader, Pharmacology/Toxicology

Date: February 17, 2006

Pfizer has purchased the rights to dalbavancin and reworked the label. The following is a response to the labeling changes.

In order to make the ratios between the animal and human AUCs look more favorable to the company, and based on the shorter half-life in animals as compared to humans, the sponsor has proposed using a 0-24 AUC from animal studies (reproductive toxicity as well as 28 and 90 day dog and rat toxicity) multiplied by 14 days in comparing to the human AUC. After a discussion with the Biopharmaceuticist, Dr. Chuck Bonapace, this approach is acceptable. However, the AUC from the hepatic impairment study (33.8 mg.hr/mL) will be used for comparison as that is derived from the one study where the once weekly dosing protocol was administered.

There are slight disagreements between the my interpretation of a NOAEL and the sponsor's according to Table 1 of the "Summary and Proposal for Dalbavancin Safety Ratios". The values I used to calculate the AUCs for the 28 and 90 day studies were from the latest day that PK was measured. I used a mean of the male and female values as there were no significant differences in pharmacokinetics with gender. In the case of the rat, the data from the two 28 day studies were also included in the means. I concur with the sponsor that the NOAEL for the 90 day dog study is the MD, 10 mg/kg. The following table summarizes the sponsor's data versus my calculations.

Study	Animal Dose mg/kg/day	Cumulative AUC (sponsor) mg.h/L	Cumulative AUC Reviewer ug.h/mL	Safety ratio Sponsor	Safety ratio reviewer
Seg I rat NOAEL	15	(b) (4)	&	(b) (4)	1.2
Seg I rat adverse effects	45		&		3.5
Seg II rat NOAEL	15		30422 ^{\$}		0.9
Seg II rat adverse effects	30		57134 ^{\$}		1.7
Seg II rabbit NOAEL	15		&		0.7
DX28 rat NOAEL	10		18921		0.6
DX28 rat adverse effects	40		84228		2.5
DX90 rat NOAEL	5		15905		0.5
DX90 rat adverse effects	10		29456		0.9
DX90 dog NOAEL	10		40509		1.2
DX90 dog adverse effects	40		158067		4.7

& used the same numbers as the sponsor.

^{\$} AUCs were calculated by the reviewer using the least squares method based on plasma levels at 0, 1, 2, 4, 8 and 24 hours.

The changes in the wording of the text in the pharm/tox sections do not alter the intent, and are compatible with the standard format. In the Animal Pharmacology section, the ratio at 40 mg/kg needs to be added (approximately 5 fold). Thus, the text there should read:



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/s/

Wendelyn Schmidt
2/22/2006 04:09:34 PM
PHARMACOLOGIST

Terry Peters
2/24/2006 04:14:44 PM
PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-883
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	December 21, 2004
PRODUCT:	Dalbavancin
INTENDED CLINICAL POPULATION:	Patients with skin/skin structure infections
SPONSOR:	Vicuron Pharmaceuticals, Inc.
DOCUMENTS REVIEWED:	Electronic NDA
REVIEW DIVISION:	Division Anti-Infective Drug Products (HFD-520)
PHARM/TOX REVIEWER:	Wendelyn J. Schmidt, Ph.D.
PHARM/TOX SUPERVISOR:	Robert Osterberg, Ph.D.
DIVISION DIRECTOR:	Janice Soreth, M.D.
PROJECT MANAGER:	Christopher Davi

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

1. Recommendations

- 1.1 Recommendation on approvability
From the pharmacology/toxicology perspective, the non-clinical studies were adequate for approval.
- 1.2 Recommendation for nonclinical studies
There are none at this time. The sponsor is undertaking studies in juvenile animals.
- 1.3 Recommendations on labeling:



(b) (4)

2. Summary of nonclinical findings

- 2.1 Brief overview of nonclinical findings
- 2.2 Pharmacologic activity
- 2.3 Nonclinical safety issues relevant to clinical use

Dalbavancin is a lipoglycopeptide which interferes with bacterial cell wall formation and is active against Gram-positive bacteria. Early studies on the safety pharmacology of dalbavancin showed no effects on respiration, body temperature or behavior at doses up to 20 mg/kg in the mouse, rat, and or rabbit. Later toxicology studies at doses up to 80 mg/kg in the rat and 60 mg/kg in the dog, showed no clinical signs in the rat, while dogs at 40 to 60 mg/kg showed a histaminic response (ear congestion, mucosal pallor) with salivation.

As other compounds in the class have been shown positive in the hERG assay (see table below), a full preclinical cardiac work-up with dalbavancin was requested.

Class effects with glycopeptides					
Drug	Histamine response	HERG +	Δ BP	EKG	Human cardiac
Dalbavancin	Yes	NO	Yes * (\downarrow)	No	NO
Oritivancin	Yes	Yes	Yes (\uparrow)	No	No
Vancomycin	Yes	Yes	?	?	No
TD6424	Yes	Yes	No	Yes/No	?

*A decrement in BP was noted in some studies, but not all.

The hERG assay was negative; the maximum level feasible for testing was below plasma levels seen in the clinic. Similarly, the Purkinje fiber assay was negative, but the positive control did not show an effect. Blood pressure responses were variable: some studies showed a decrement during the first few hours (probably attributable to a histaminic response), while other studies did not. Anesthetized dogs did not show a change in blood pressure or ECG traces at doses up to 20 mg/kg nor did telemeterized dogs at doses up to 60 mg/kg. Finally, no evidence of QT interval prolongation has been noted in human clinical trials. In conclusion, dalbavancin does not appear to affect cardiac electrical function.

The pharmacokinetics of dalbavancin have been explored in mouse, rat, rabbit, dog, mini-pig and human. In most of the PK studies, the number of animals investigated is low (one or two/timepoint) so the values generated should be treated more like an estimation, not an absolute. Between the pharmacokinetic and toxicokinetic studies, there do not appear to be any gender effects on dalbavancin plasma levels. Given the long half-life and redistribution of dalbavancin, the collection period of data is critical. Plasma half life, depending on how long the drug was followed in the plasma, was in the range of 1-3 weeks in rats and dogs. Tissue residence time in the dog was over 6 months. Dalbavancin was widely distributed into tissues, but did not cross the blood brain barrier. As there does not seem to be much of a contribution of metabolites to the plasma levels, method of detection should have a minimal impact on the final values (which was the case with the rat). Accumulation was seen, as one would expect, with multiple daily dosing in rat and dog. AUCs are roughly linear with dose. The AUC at the NOAEL in rat and dog ranges from approximately 1100 to 2200 ug.h/mL. Similarly, the range of AUCs at the lowest toxic level ranged from 2100 to 5100 ug.h/mL, a slight overlap. The human AUC to infinity ^{(b) (4)} following a 1000 mg iv dose then a week later by 500 mg iv. is approximately 26000 mg.hr/L. At the lowest toxic level in rats and dogs, the AUC at the end of the treatment period is approximately 5-10 fold higher in humans than in dogs or rats. Excretion is via both urine and feces. The hydroxyl-dalbavancin metabolite is seen primarily in the urine.

The toxicologic profile of dalbavancin is similar in rats, dogs and humans. Injection site damage (necrosis, erythema, etc at the tail vein) was a dose-limiting toxicity in the rat in the 1 and 3 month intravenous studies. Both rats and dogs showed elevations of ALT/AST along with periodic alterations in cholesterol, protein and triglyceride plasma levels. The elevations in AST/ALT persisted in the dog for more than 15 months after the end of the treatment period, which is not unexpected given the long residence time of the compound in the liver. Microscopic damage included hepatocellular necrosis,

vacuolization and degeneration. In the 3 month dog, damage was described as centrilobular necrosis and hepatocellular dissociation. In the kidney, elevations in BUN were seen in rat and dog which persisted through 15 months post-dosing in dog (slowly diminishing severity) and was demonstrated microscopically as tubular vacuolization/ degeneration/necrosis. In the 3 month dog, the severity of damage to the kidney was increased to mostly tubular necrosis, and glomerulonephritis was also observed. Pancreatic vacuolization/degeneration/ apoptosis and acinar atrophy were noted with greater frequency in the rat. The relevance of this finding is toxicologically insignificant. No new toxicities arise with longer dosing periods, although some of the microscopic damage became more severe.

The clinical toxicities seen in the human trials have included gastrointestinal effects (nausea/vomiting/constipation/diarrhea), anemia, and liver enzyme elevations. Both rats and dogs appear predictive for the human, especially if the drug is administered by a catheter in the rat. The dosing schedule is such that the animals are exposed to a longer duration with daily dosing as opposed to the 2 dose (once weekly) schedule that humans receive.

The reproductive toxicity studies in rat and rabbit were adequate. The fertility index in the rat was decreased at 45 mg/kg/day, while the NOAEL was 15 mg/kg/day. No embryotoxic or embryolethal effects were seen in the Segment II study in the rabbit at doses up to 15 mg/kg/day during organogenesis. In the rat, the fetal NOAEL was 15 mg/kg/day with delayed ossification in the sternbrae and skull. In the segment III rat study, increased lethality (stillborn/unexplained early death in 1st week) was seen at the HD (30 mg/kg/day to the dams). No effects on developmental milestones or the F2 generation were observed. The NOAEL was 15 mg/kg/day. Dalbavancin levels in both the pups' plasma and mothers' milk were approximately 1/10 of the maternal plasma levels of compound.

Dalbavancin was negative for mutagenicity and clastogenicity in the standard battery of assays. Dalbavancin was not irritating to skin or eyes and did not cause immunomodulation.

Conclusions: The exposure to dalbavancin is 5-10 fold less in the animals at toxic levels than the plasma levels seen clinically. The toxicities were similar in humans and the animal models (rat and dog). The main toxicities to injection site, kidney and liver are monitorable, although the changes in the liver and kidney persist for months after administration.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21883

Review number: 1

Sequence number/date/type of submission: December 21, 2004

Information to sponsor: Yes () No (X)

Sponsor and/or agent:

Vicuron Pharmaceuticals, Inc.
455 South Gulph Road
Suite 310
King of Prussia, PA 19406

Manufacturer for drug substance:

(b) (4)

Reviewer name: Wendelyn J. Schmidt, Ph.D.

Division name: Division of Anti-Infective Drug Products

HFD #: 520

Review completion date: 4/7/05, revised 8/16/05

Drug:

Generic name: Dalbavancin

Code name: VER001, BI-397, V-glycopeptide

Chemical name: (b) (4)

Molecular formula/molecular weight: Main component: mw =1817

Relevant INDs/NDAs/DMFs: IND 60613

Drug class: Glycopeptide antibiotic

Indication: Treatment of skin and skin structure infections

Clinical formulation: (b) (4) 500 mg

Route of administration: Intravenous infusions

Proposed use: “Dalbavancin is indicated for the treatment of adult patients with the following infections caused by susceptible strains of the designated organisms in the conditions listed below:

Complicated skin and skin structure infections caused by *Staphylococcus aureus* including methicillin-resistant and MDR strains, *Streptococcus pyogenes*, *Streptococcus agalactiae*, (b) (4)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Safety Pharmacology

1. Study 021107.WTD: Effects of Dalbavancin on cloned hERG channels expressed in mammalian Cells. (Reviewed with serial #112, W. Schmidt)
2. Study 1547/VRS/02:Effects of Dalbavancin on Action Potential Duration (APD) in Rabbit Purkinje Fibers. (Reviewed with serial # 065/074, W. Schmidt)
3. Study (b) (4) 971102: BI 397: Behavioral Irwin test and effect on body temperature following single intravenous administration in mice. (Reviewed with serial #000, K. Seethaler)
4. Study (b) (4) 971106: BI 397: Evaluation of effect on the autonomic nervous system following single intravenous administration in conscious rats. (Reviewed with serial # 000, K. Seethaler)
5. Study (b) (4) 981149: BI 397: Evaluation of effect on respiration in the unrestrained conscious rat following single administration by the intravenous route. (Reviewed with serial # 000, K. Seethaler)
6. ABVW-0001: A Cardiovascular safety study of Dalbavancin (VER001) administered to telemetered Beagle dogs. (Reviewed in NDA).
7. Study (b) (4) 971104: BI 397: Evaluation of effect on platelet aggregation induced by collagen and arachidonic acid on rabbit platelets. (Reviewed in serial #000, K. Seethaler)
8. Study (b) (4) 971103: BI 397: Effect on bleeding time following single intravenous administration in the rat. (Reviewed in serial # 000, K. Seethaler)
9. Study (b) (4) 981150: BI 397: Evaluation of haemodynamic effects following intravenous dosing in the anaesthetized dog. (Reviewed in serial #000, K. Seethaler)
10. Study (b) (4) 990417: BI 397: Evaluation of haemodynamic effects following intravenous dosing in the anaesthetized dog. (Reviewed in serial #000, K. Seethaler).
11. Study (b) (4) 990481: Action of noradrenaline on hypotensive effects of BI 397 (batch 011) in anaesthetized dogs. (Reviewed in serial #000, K. Seethaler).

Pharmacokinetics: (All summarized in the NDA)

1. Study GE028-03: Dalbavancin uptake in mouse macrophage cell line (5774).
2. Report (b) (4) -116D-0301B: Distribution of ¹⁴C-Dalbavancin in rat livers by autoradioluminography and microradiography.
3. Study (b) (4) 980208: [³H]-BI 397. Whole-body autoradiography study in the rat after single intravenous administration.
4. Study (b) (4) 012140: A study of quantitative tissue distribution and bile excretion following single continuous intravenous infusion of ³H Dalbavancin in male rats.
5. Report (b) (4) -116D-0301: Distribution of ¹⁴C-Dalbavancin in dog livers by autoradioluminography and microradiography.

6. ABVZ-0002: Dermal uptakes of ^{14}C -Dalbavancin following intravenous administration to (b)(4) minipigs.
7. Wise 2000: Report on in vitro studies on BI397 conducted at (b)(4)
8. GE058-04: Protein binding of MAG and OH-Dalbavancin.
9. GE023-04: Pharmacokinetic of Dalbavancin in mouse pilot IV study.
10. GE063-04: Pharmacokinetic of Dalbavancin in mouse pilot IP study.
11. Study GE027-99: BI 397 Pharmacokinetics in the rat.
12. Study GE035-99: BI 397 Pharmacokinetics in the rabbit.
13. Study (b)(4)971101: BI 397: Pharmacokinetics study after a single intravenous administration in the dog.
14. Report 01098-XBL03135: Mass balance and metabolism of ^{14}C -Dalbavancin following a single IV infusion of 20 mg/kg to male rats.
15. XBL03131-RPT01096: Mass balance of ^{14}C -Dalbavancin following a single IV dose of 20mg/kg to the dog.
16. RPT01059-XBL03817: In vivo study of Dalbavancin as inducer of rat Cytochrome P450 enzymes.
17. Study GE047-01: Pharmacokinetics and excretion of Dalbavancin in the rat.
18. (b)(4) Study-XBL012139: VER001: A mass balance study following a continuous intravenous infusion of ^3H -VER001 in male rats. (Reviewed with serial # 065/074, W. Schmidt)
19. Study XBL03135-RPT01058: mass balance and metabolism of ^{14}C -Dalbavancin following a single IV infusion of 20 mg/kg to male rats.
20. XBL03131-RPT01038: mass balance of ^{14}C -Dalbavancin following a single IV dose of 20mg/kg to the dog.

Toxicology:

1. Study (b)(4)971094: Single dose toxicity study in mice treated with the test article BI 97 by oral and intravenous routes. (Reviewed in serial #000, K. Seethaler)
2. Study (b)(4)971093: Single dose toxicity study in rats treated with the test article BI 397 by oral and intravenous routes. (Reviewed with serial # 000, K. Seethaler)
3. Study (b)(4)971095: Dose range-finding study in Sprague Dawley CrI:CD (SD)BR rats treated with the test article BI 397 administered by intravenous route at the doses of 0, 25, 75 and 150 mg/kg/day for two consecutive weeks. (Reviewed with serial # 000, K. Seethaler, W. Schmidt)
4. Study (b)(4)971096: 4-week intravenous toxicity study in Sprague Dawley CrI:CD (SD) BR rats treated with the test article BI 397 administered by intravenous route at the doses of 0, 5, 10, 20 and 40 mg/kg/day followed by 4 weeks of recovery. (Reviewed with serial #000, K. Seethaler, W. Schmidt)
5. Study RBM980831: 4-week repeated dose toxicity study in Sprague Dawley CrI:CD (SD) BR rats treated with the test article BI 397 administered by intravenous route at the doses of 0, 10, 20, 40 and 80 mg/kg/day followed by 4 weeks of recovery. (Reviewed with serial # 000, K. Seethaler, W. Schmidt)
6. Study (b)(4)990942: BI397: Pilot study in no-pregnant female rabbits by intravenous route.

7. Study (b) (4) 971097: Dose range-finding study in Beagle dogs treated with the test article BI 397 administered by intravenous route. (Reviewed with serial # 000, K. Seethaler, W. Schmidt)
8. Study (b) (4) 990975: 2-week toxicity study in Beagle dogs treated with the test article BI 397 administered by intravenous at the doses of 0 and 10 mg/kg/day.
9. Study (b) (4) 971098: 4-week repeated dose toxicity study in Beagle dogs treated with the test article BI 397 administered by intravenous route at the doses of 0, 5, 10, 20 and 40 mg/kg/day, followed by 4 weeks of recovery at the dose of 20 mg/kg/day. (Reviewed with Serial # 000, K. Seethaler, W. Schmidt)
10. Study (b) (4) 980779: 4-week repeated dose toxicity study in Beagle dogs treated with the test article BI 397 administered by intravenous route at the doses of 0, 10, 20 and 40 mg/kg/day, followed by 4 weeks of recovery at the dose of 40 mg/kg/day, with additional group of animals treated at 60 mg/kg/day. Reviewed with serial # 000, K. Seethaler, W. Schmidt)
11. 168-002: A three month subchronic toxicity study with Dalbavancin (VER001) in Sprague Dawley rats. (Reviewed with serial # 078, W. Schmidt)
12. 168-003: A three month subchronic toxicity study with Dalbavancin (VER001) administered via intravenous injection to Beagle dogs. (Reviewed with NDA)

Genetic Toxicology

1. Study (b) (4) 971099: Study of the capacity of the test article BI 397 to induce gene mutation in v79 Chinese hamster lung cells. (Reviewed with serial # 000, K. Seethaler)
2. Study (b) (4) 980514: Study of the capacity of the test article BI 397 to induce chromosome aberrations in Chinese hamster ovary cells (CHO). (Reviewed with serial # 000, K. Seethaler)
3. Study (b) (4) 990751: Micronucleus induction in bone marrow cells of mice treated by intravenous route with the test article BI 397. (Reviewed with serial # 000, K. Seethaler)

Reproductive Toxicology

1. Study (b) (4) R10430: Fertility and early embryonic development by intravenous route in rats. (Reviewed with serial # 029/045, W. Schmidt)
2. Study (b) (4) 990790: Preliminary embryo-fetal development study in CrI:CD (SD) BR rats of the test article BI 397 administered by intravenous route at the dosages of 0, 5, 15, 45 mg/kg/day.
3. Study (b) (4) 990752: Preliminary embryo-fetal development study in New Zealand white rabbits of the test article BI 397 administered by intravenous route at the dosages of 0, 7.5, 15, 30 mg/kg/day.
4. Study (b) (4) R09070: BI 397 embryo-fetal development study in rats by intravenous route. (Reviewed with NDA)
5. Study (b) (4) R09080: embryo-fetal development study in rabbits by intravenous route. (Reviewed with serial # 029/045, W. Schmidt)
6. 622-002: Intravenous developmental and perinatal/postnatal reproduction toxicity study of Dalbavancin (VER 001) in rats, including a postnatal behavioral/functional evaluation. (Reviewed with NDA)

Special Toxicology Studies

1. 622-010: Intravenous repeated dose 28-day immunotoxicity study of Dalbavancin (VER001) in rats. (Reviewed with NDA).
2. Study (b) (4) 980119: Skin sensitization test in guinea-pigs treated with the test article BI 397. (Reviewed with Serial # 000, K. Seethaler).
3. Study (b) (4) 980117: Acute dermal irritation study in New Zealand White rabbits treated with the test article BI 397/011. (Reviewed with Serial # 000, K. Seethaler).
4. Study (b) (4) 980118: Acute eye irritation study in New Zealand White rabbits treated with the test article BI 397/011. (Reviewed with Serial # 000, K. Seethaler).

Studies not reviewed within this submission: None

3.2 PHARMACOLOGY:

3.2.1 Brief summary:

The Pharmacology section of this NDA is reviewed by the Microbiologist (Dr. Fred Marsik). Dalbavancin is a lipoglycopeptide which interferes with bacterial cell wall formation and is active against Gram-positive bacteria.

3.2.3 Secondary pharmacodynamics: None submitted.

3.2.4 Safety pharmacology:

Most of these studies were reviewed in the initial submission by Dr. K. Seethaler in 2001 and are discussed in the following summary. Further studies on the cardiac effects, particularly of possible changes in the QT interval were investigated later in the clinical development of dalbavancin and are reviewed below.

Dalbavancin was tested in mouse, rat, and rabbit models for effects on respiration, body temperature, behavioral changes, and bleeding times. At doses of up to 20 mg/kg as a single intravenous dose, there were no effects observed. These doses were inadequate to elucidate toxic effects, as in the single dose toxicity studies, changes were not observed until doses of at least 93 mg/kg in the rat and 200 mg/kg in the mouse. At concentrations of up to 1 mM dalbavancin, no inhibition of platelet aggregation was observed. At the doses tested, which were similar to those in humans, no clotting problems would be expected, but no information on effects at higher doses were obtained.

The possible effects on cardiac parameters were tested both in vitro and in vivo. The effects on the ether-a-go-go (hERG) channels were negligible with dalbavancin at the maximum feasible dose; however, the dose was approximately 1/10 of the plasma levels seen clinically (180 ug/mL). The study on isolated Purkinje fibers had a large baseline drift and showed miniscule effects with the positive control. Neither of the two studies in anesthetized dog nor the telemeterized dog study with up to a single dose of 60 mg/kg intravenously showed a significant effect on blood pressure, heart rate or QTc interval. While some of the individual studies are not definitive, the overall conclusion is that dalbavancin does not affect cardiac conduction or circulatory parameters.

Cardiovascular effects:

1. A cardiovascular safety study of dalbavancin (VER001) administered to telemetered beagle dogs. Study # ABVW-0001.

Conducted at:

(b) (4)

Date initiated: 8/13/03

GLP: YES QA: YES

Test article: Dalbavancin, Lot # 285048

Vehicle: 5% dextrose

Animals: 4 telemeterized, conscious female beagle dogs

Dose: 0, 30, 40, 60 mg/kg i.v. on day 1, 8, 15, 22, 29 (control only on day 1, 29) at 2.0 mL/kg over 30 minutes.

Parameters measured: Clinical observations, body weight, blood pressure (every 5 minutes, during infusion, every 15 minutes for 6 hours, then every hour to 24 hours post-dose), heart rate, 20 second ECG tracings over 24 hours (every 15 minutes during infusion, every 30 minutes through 6 hours, then hourly), TK (Prior to infusion and end of infusion on days 1, 2, 3, 6, 8, 9, 10, 13, 15, 16, 17, 20, 22, 23, 24, 27, 29, 36, and 50; method used: LC/MS/MS).

Note: A positive control study with sotalol (0, 2, 5, 20, 40 mg/kg) had been conducted in these dogs in May 2003. A dose dependent pattern of onset and duration of prolongation was observed, with prolongation of QTc of 16%, 27%, and 32% at doses of 5, 20 and 40 mg/kg. So although a concurrent positive control was not run, these dogs had responded another compound within a few months of this study.

Results:

Mortality and clinical signs: All dogs survived to the end of the study. Observations included head shaking, hives and erythema which became more frequent and widespread with multiple/higher doses.

Body weight: Body weights did not change significantly over the course of the study.

Hemodynamic response: There were no significant changes in hemodynamic response between vehicle and dalbavancin.

ECG: There were no significant differences in the QTc interval in treated dogs as compared to controls.

Toxicokinetics: The toxicokinetic parameters are shown in the table below. The half-life was calculated at 251 ± 23 h while the clearance was 0.01264 ± 0.0033 L/hr. The human AUC at 1000 mg was estimated by the sponsor to be approximately 230000 mg.h/L. Detectable levels of parent compound were seen predose for the 40 and 60 mg/kg sessions. OH-Dalbavancin was either below the level of quantitation or at negligible levels.

Toxicokinetics in the telemeterized dog		
Dose (mg/kg)	Cmax (mg/L)	AUC (mg.h/L)
30	642 ± 266	16757 ± 4896
40	1048 ± 153	25242 ± 1538
60	1492 ± 564	38730 ± 8893

Conclusions and comments:

In this adequately conducted study, the doses were adequate based on both PK and toxicology considerations. There were no effects on cardiac parameters including QTc interval.

3.2.5 **Pharmacodynamic drug interactions:** Not studied.**3.3 PHARMACOKINETICS/TOXICOKINETICS**

3.3.1 Brief summary

The majority of the ADME studies have been discussed in previous reviews. However, the entirety of the package is re-summarized here for convenience. Dalbavancin has a long half-life and persists in the animals for long periods of time (detectable levels are still present in the dog at 181 days after a single dose). Drug does not localize into fat, but remains widely distributed, with the exception of the CNS. Metabolism is minimal to moderate and excretion is both via the urine and feces.

3.3.3 Absorption:

The pharmacokinetic parameters for single dose and TK studies are shown in the following table. One of the shortcomings of the single dose studies was that usually only a single gender of animals was examined. However, when combining the single dose data with that generated in the TK studies, a fuller picture can be derived. The differences in AUC/Cmax were not huge when using different methods of detection (e.g. HPLC, antibiotic activity or radiolabel), which shows that metabolites do not make a major contribution to plasma levels of drug.

Pharmacokinetic parameters with single intravenous doses of Dalbavancin									
Ref #	Species	N	Sex	Dose mg/kg	Analysis method	Time course	Cmax mg/L	AUC mg.hr/L	T ½ h
9	ICR mouse	3	F	5	Micro	0.08-144 h	53 ± 2	200	---
				20	Micro		241 ± 13	1071	62
10	ICR mouse	3	F	5*	Micro	0.08-144 h	15	176	---
				20*	Micro		71	848	53
11	SD rat	5	M	20	Micro	0.05-144 h	333 ± 32	2745 ± 441	14 ± 1
17	SD rat	3	M	20	LC/MS/MS	0.08-248 h	323	3067	124
4	SD rat	3	M	20	³ H	0.08-1680 h	53.4	2180	321
12	NZW rabbit	5	M	20	Micro	0.05-72 h	372 ± 43	2231 ± 196	14 ± 1
13	Beagle dog	3	M	5	HPLC	0.08-120 h	51 ± 5	1030 ± 93	25 ± 5
			F				82 ± 9	1356 ± 107	25 ± 5
19	Beagle dog	4	M	20	¹⁴ C	0-181 d	233 ± 20	6515 ± 405	646 ± 96
1	(b) (4) mini-pig	1	F	10	¹⁴ C	0.25-648	109 ± 16	3696 ± 319	91 ± 18

*intraperitoneal dosing; --- indicates parameter not calculated

The toxicokinetic parameters are shown in the table below. Timecourse of observations was over 24 hours. Analysis was by HPLC. There are several points to this table. First, there are no consistent differences between males and females in either

rat or dog. Secondly, given the low number of animals, there was little difference between studies in the AUC values (usually within 2 fold). Dalbavancin accumulated with plasma levels increasing by as much as 2 fold between day 1 and 28 in the rat, but little further accumulation was seen between days 28 and 90.

Toxicokinetics of Dalbavancin in rats and dogs								
Species	Schedule	Dose mg/kg	Day	Males		Females		
				Cmax ug/mL	AUC ug.h/mL	Cmax ug/mL	AUC ug.h/mL	
SD rat	DX28d N=2/time-point	5	1	---	280	36	429	
			23	41	528	62	642	
		10	1	70	1056 ^a /787 ^b	78	731/1062	
			23	94	1258/1300	124	1431/1417	
		20	1	142	1631/1853	140	1213/2308	
			23	236	3293/3756	194	2648/4001	
		40	1	248	2688/4134	216	2260/4616	
			23	366	5403/7837	472	4082/6743	
		80	1		----/8830		----/8204	
			23		---/15220		----/11366	
		DX90d N=1/time point	5	28	105	1041	89	895
				90	112	1173	97	1100
	10		28	231	1839	196	1759	
			90	171	2159	155	2049	
	40		28	548	4837	511	5477	
			90	---	---	---	---	
	Beagle dog	DX28 N=1/time point	5	1	40	464	66	690
				28	45	664	79	993
10			1	96 ^c /114 ^d	1086/1541	92/100	1135/1344	
			28	123/141	1576/2455	114/137	1647/2019	
20			1	223/280	2782/3735	200/172	2744/2686	
			28	240/505	4323/5592	292/444	4423/4702	
40			1	506/538	5073/6836	478/598	5188/6334	
			28	547/900	6491/13004	544/576	7336/13201	
60			1	---/991	---/11749	---/858	---/10733	
			28	---/1190	---/14737	---/987	---/13286	
DX90d N=4			5	1	82	673	81	630
				28	118	1342	122	1424
		90		108	1238	102	1110	
		10	1	151	1351	159	1354	
			28	257	3182	221	2582	
			90	237	3193	207	2594	
		40	1	608	5448	667	6168	
			28	875	11719	834	11714	
	90		733	10573	895	12008		

^a Study # (b) (4) 971096, ^b study # (b) (4) 980831, ^c study # (b) (4) 971098, ^d study # (b) (4) 980779

3.3.4 Distribution:

Distribution was investigated systemically in the rat, dog, and in relation to the skin, mini-pig. Almost all organs had detectable levels of label, whether by LSC counting or by autoradiography. Kidney, liver and aorta showed higher levels than plasma at both early time points through 70 days post-dose in the rat (for example, 4.3% of the total dose was still present in the liver at day 70). Brain and spinal cord showed minimal levels of label. Both skin in the rat tissue distribution study and skin in the mini-pig study showed significant levels after ¹⁴C-dalbavancin administration at 10 or 20 mg/kg (minipig concentrations were 5-6% of the administered dose on day 1 and 1-2% by day 7).

3.3.5 Metabolism

The major metabolites mentioned were mannosyl aglycone dalbavancin (MAG), and hydroxyl dalbavancin (OH-Dalbavancin). The only information included in the non-clinical section on protein binding was on these metabolites; both of which were about 72% protein bound in human serum. In the report from Wise (Ref # 7) dalbavancin binding by ultracentrifugation with either human serum or albumin was between 87 and 89%. In the rat liver, approximately 3.4% of the total dose was found as parent compound at day 7 post-dose, while no OH-dalbavancin was found and < 0.1% of the total was the MAG form (Day 7 through Day 120 post-dose). Dog liver also showed only parent compound and MAG. Parent compound in the dog declined from 9% of the radioactivity on Day 70 to 2% at day 161/181 while MAG remained a constant 2-3% of the radioactivity present in the liver. In dog urine, the majority of radioactivity between Day 1 and Day 70 was associated with parent compound. The major metabolite was the OH-dalbavancin, with 4 other metabolites (including MAG) detected, all of which were less than 0.4% of the total dose by Day 2 (data presented below). In dog feces, parent drug was the major component; all metabolites accounted for less than 0.1% of the total dose from day 1. Parent drug also predominated in plasma, with a M8 metabolite accounted for between 0.4 and 9.4% of the detectable radioactivity between 0.5 h and day 70.

Rat liver microsomes were neither induced nor suppressed with dalbavancin administration. Further, dalbavancin was not metabolized significantly by liver microsomes.

Percent Distribution of ¹⁴C-Dalbavancin Metabolites in Urine After a Single Dose of ¹⁴C-Dalbavancin to Male Dogs

Metabolite ID	R, Range (min)	Day 1		Day 2		Day 3		Day 4		Day 5	
		%ROI	%Dose	%ROI	%Dose	%ROI	%Dose	%ROI	%Dose	%ROI	%Dose
M1	3-4.25	3.54%	0.87%	1.20%	0.14%	0.51%	0.03%	2.37%	0.08%	5.89%	0.11%
M2 (MAG)	26.25-28.25	13.25%	3.25%	3.38%	0.40%	0.82%	0.05%	0.79%	0.03%	0.60%	0.01%
M3	32.75-34.00	4.97%	1.22%	1.05%	0.12%	ND	ND	ND	ND	ND	ND
M4	34.25-35.25	8.99%	2.20%	1.27%	0.15%	0.51%	0.03%	ND	ND	1.20%	0.02%
M5 (OH-dalbavancin)	35.25-36.75	25.52%	6.25%	30.86%	3.61%	37.77%	2.32%	36.93%	1.22%	34.98%	0.63%
M6	38.25-38.25	0.50%	0.12%	0.51%	0.06%	ND	ND	ND	ND	ND	ND
dalbavancin	52.5-59.5	43.22%	10.59%	61.74%	7.22%	60.39%	3.71%	59.92%	1.98%	57.33%	1.03%
Total		99.99%	24.50%	100.01%	11.70%	100.00%	6.15%	100.01%	3.31%	100.00%	1.80%
Metabolite ID	R, Range (min)	Day 6		Day 7		Day 14		Day 28		Day 70	
		%ROI	%Dose	%ROI	%Dose	%ROI	%Dose	%ROI	%Dose	%ROI	%Dose
M1	3-4.25	8.41%	0.09%	12.70%	0.10%	26.99%	0.10%	28.57%	0.07%	41.58%	0.04%
M2 (MAG)	26.25-28.25	0.90%	0.01%	1.44%	0.01%	5.67%	0.02%	6.33%	0.02%	9.18%	0.01%
M3	32.75-34.00	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M4	34.25-35.25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M5 (OH-dalbavancin)	35.25-36.75	29.58%	0.30%	30.74%	0.25%	29.14%	0.11%	21.34%	0.05%	15.05%	0.02%
M6	38.25-38.25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
dalbavancin	52.5-59.5	61.11%	0.63%	55.12%	0.45%	38.19%	0.14%	43.76%	0.11%	34.18%	0.03%
Total		100.00%	1.03%	100.00%	0.81%	99.99%	0.37%	100.00%	0.25%	99.99%	0.10%

ND = Not detected
 NA; not applicable

3.3.6 Excretion

The following table shows the urinary and fecal levels of dalbavancin in rat and dog. The main point here is that excretion occurs over a LONG period of time. For example, in the dog, 15.9% of the dose was associated with the carcass at day 70 and 7.2% was still there at day 181. Further, based on the tissue distribution studies, the drug is not just associated with fats, but generally distributed. This may be associated with protein binding/turnover, as the protein binding of dalbavancin is > 80%.

Ref. #	Species	Dose mg/kg	Last day of collection	Method of detection	% dose in urine	% dose in feces	% in carcass	% of total recovered
17	Rat	20	10	LC/MS/MS	34.5%	---	4.3%	---
18	Rat	20	70	³ H	44.0%	23.1%	4.5%	92-95%
19	Dog	20	181	¹⁴ C	65.3%	9.5%	12.1%	92%

3.3.7 Pharmacokinetic drug interactions

Cytochrome P450 enzymes were neither induced nor inhibited by dalbavancin. No other interactions were investigated.

3.3.10 Tables and figures to include comparative TK summary (see above).

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology:

The following table briefly summarizes the data on the toxicology studies conducted with intravenous dalbavancin. Overall, the target organs for toxicity were the liver and kidney. Damage at high doses included necrosis and enzyme elevations for the liver, BUN and creatinine increases with tubular necrosis in the kidneys. In the dog in particular, LFTs and renal serum chemistry markers remained elevated for months after the cessation of dosing, reflecting the persistence of dalbavancin in tissues like the liver. Injection site damage was severe enough to stop dosing in rats, and was present in dogs. Lymph nodes and pancreas (primarily microscopic evidence of vacuolization) were also affected at higher doses for long periods of administration.

Intravenous studies conducted with dalbavancin						
Species	Schedule	Doses mg/kg	Target organs	LD or NOAEL mg/kg	AUC* at NOAEL ug.h/mL	AUC at Lowest Toxic level
CD-1 Mouse	1X	160, 200, 250	CNS	LD50= 200	---	---
SD rat	1X	93, 102, 112	CNS	LD10 =93	---	---
SD rat	DX14	25, 75, 150	Liver	NOAEL= 25 LLD = 25		
SD rat	DX 28	10, 20, 40, 80	Liver, kidney, Injection site	NOAEL= 10	D1 = 909 D23= 1351	D1 = 1751 D23 = 3424
SD rat	DX 90	5, 10, 40	Liver, kidney injection site, pancreas	NOAEL < 5	D28 = 968 D90= 1136	D28 = 1799 D90=2104
Beagle dog	DX28	5, 10, 20, 40, 60	Liver, kidney, injection site	NOAEL = 10	D1 =1442 D28 = 2237	D1 = 3210 D28= 5147
Beagle dog	DX90	5, 10, 40	Liver, kidney, injection site	NOAEL = 5	D1 = 651 D90 = 1174	D1= 1352 D90= 2893

---no values collected, * AUC values are mean of male and female (no significant differences).

Genetic toxicology:

The genetic toxicity studies conducted, HGPRT locus in Chinese hamster lungs, chromosomal aberrations in Chinese hamster ovaries, and mouse micronucleus assays (all conducted appropriately and validly), dalbavancin was neither mutagenic nor clastogenic.

Carcinogenicity: No carcinogenicity studies were necessary for this drug as use is short-term.

Reproductive toxicology:

The reproductive toxicity battery was completed adequately for this drug. In a fertility study conducted in rats, the fertility index decreased at 45 mg/kg/day (the highest dose tested). The NOAEL was the MD, 15 mg/kg/day. Accompanying histopathology included glandular atrophy in the prostate and seminal vesicles and decreased secretory material. The NOAEL in the females was 45 mg/kg/day.

No teratogenic effects were seen in rabbits at doses up to 15 mg/kg/day intravenously (maternally toxic level). Similarly, the maternal NOAEL in the rat developmental toxicity study was 45 mg/kg, the highest dose studied, while the fetal NOAEL was 15 mg/kg. Delayed ossification of sternebrae and skull were noted at 45 mg/kg.

In the Segment III study in rats, while there was minimal maternal toxicity in the HD group (other than injection site damage, a significant number of HD pups were stillborn (18.7%). In the F1 offspring, the HD pups had a decreased body weight (10% as compared to controls) and approximately twice as many pups as in the control group died during the first week. There were no differences in meeting developmental milestones in the F1 pups. There was a non-statistically significant decrease in the mating index in the HD animals. There was also a statistically significant decrease in the number of implantation in the HD (14.5/litter at HD vs. 16.6 in the controls). The NOAEL for maternal toxicity in the F0 generation was 30 mg/kg. The NOAEL for F1 generation (and F2 generation) was 15 mg/kg. Plasma levels in the pups was approximately 1/10 that in the dams and drug was secreted in mother's milk (approximately 1/10 of maternal plasma levels).

Special toxicology:

Dalbavancin was not deemed to be irritating to the eyes or skin. Additionally in the guinea pig, it did not cause sensitization. Similarly, a rat study showed no immunomodulation with 28 days of dalbavancin treatment.

3.4.2 Single-dose toxicity: The single dose toxicity studies have been previously reviewed and are included in the discussion of general toxicology.

3.4.3 Repeat-dose toxicity

1. Study # 168-003: A Three month subchronic toxicity study with dalbavancin (VER001) administered via intravenous injection to Beagle dogs.

Conducting laboratory and location: (b) (4)

Date of study initiation: June 13, 2002

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity: dalbavancin (bulk), lot # 029, 95.9% pure

Vehicle: 5% dextrose

Methods

Doses: 0, 5, 10, 40 mg/kg/day

Species/strain: Beagle dogs

Number/sex/group or time point (main study): 4/sex/dose

Route, formulation, volume, and infusion rate: intravenous, once daily

intravenous infusion over at 3 mL/min at a volume of 2 mL/kg for 90 consecutive days

Satellite groups used for recovery: 3/sex at control, HD

Age: 7-8 months

Weight: M: 8.1-12.1 kg; F: 6.6-9.2 kg

Unique study design or methodology (if any): HD males ceased dosing on day 77 and were continued on recovery. Animals were killed on either day 91 or day 506.

Observation times and results:

Mortality (twice daily): Two of the 4 HD male dogs were sacrificed moribund on days 57 and 64. All other animals survived to scheduled sacrifice.

Clinical signs (twice daily, physical exams monthly): Changes were observed only in the HD dogs. In the males, signs consisted of cold to touch, decreased activity, prostration, bloodshot eyes, increased salivation, thin, post-dose vocalization, reddened skin after dosing, swelling of head and feet, vomiting, and soft stools. High-dose females showed the same signs with the exception of cold to touch, prostration and the addition of dehydration.

Body weights (weekly): By the end of the first week, body weights in the HD males had begun to decrease, with the greatest difference at Day 56 (decreased 25% as compared to controls). At the end of the recovery period, body weights were still decreased by 20% in the males. Similar decrements in body weights were seen in the HD females during the treatment period; however, during the recovery there were no remarkable differences in body weights between treatment and control dogs.

Food consumption (weekly): Food consumption was decreased by approximately one quarter as compared to controls; however, by the end of the recovery period, food consumption was similar in treated and control groups.

Ophthalmoscopy (Monthly): There were no differences noted in the observations of the treated and control dogs.

EKG (pretest, study day 1 at 0.5 and 2 h post-dose, monthly, included blood pressure, heart rate): On Day 1, mean blood pressure decreased by approximately 30% in the HD males within the first hour after drug administration; changes in blood pressure were not significant thereafter. There were no consistent changes in QT interval with treatment.

Hematology (Pretest, monthly through 15 months of recovery): Changes affecting RBC parameters and platelets were slightly greater in magnitude and duration in males than in females. White blood cell numbers were not significantly altered with treatment. Platelet numbers fell slightly at the HD during treatment (up to 30% decrement at HD as compared to controls), then increased to up to 25% in females and 30% in males throughout the recovery period (not always statistically significant). RBC numbers in the HD animals began to decrease at the end of the treatment period (30% decrease in males, 25% decrease vs. controls in females, statistically significant). Decreases tapered off to not significantly different from controls at 12 months into the recovery period for males, 7 months in females. No significant differences in reticulocytes (NRBCs) were noted.

Clinical chemistry (Pretest, monthly): The changes in clinical chemistry parameters are shown in the following table. The primary effects were seen in the kidneys and liver, beginning at the first timepoint monitored and continuing through the end of the recovery period 15 months later. Liver enzymes were elevated in the MD males females only at month 3 (assume day 61) and day 91 (2-4 fold elevations). Other parameters that were periodically elevated included cholesterol, total bilirubin, triglycerides and ALP.

Clinical Chemistry parameters in HD dogs treated for 3 months with dalbavancin as compared to concurrent controls						
Parameter	Males			Females		
	First observed	Return to baseline	zenith	First observed	Return to baseline	Zenith
Total protein	2 mos (↓14%)	Rec 15 mos	Rec 1 mo ↓19%	2 mos ↓10%	Rec 4 mos	91 d ↓12%
BUN	2 mos ↑3X	> Rec 15 mos	2 mos ↑4X	1 mo ↑2X	> Rec 15 mos	91d ↑4X
Creatinine	1 mo ↑2X	> Rec 15 mos	2 mos ↑4X	1 mo ↑83%	Rec 6 mos	91D ↑4X
ALT/AST	1 mo, ↑2-3X	> Rec 15 mos	D77-Rec 3 mos, >>10X	1 mo, ↑2X	>Rec 15 mos	91D, >>10X

Urinalysis (Pretest, monthly): There were no consistent changes with treatment.

Gross pathology:

In the early death HD males, the kidneys were grey. In the HD females at day 91 (end of treatment), both the liver and kidneys were pale. At the end of the recovery period, 3/5 males had enlarged prostates, while there were no findings in the females.

Organ weights (adrenals, brain, heart, liver, lungs, ovaries, pituitary gland, spleen, testes and thymus): The changes in organ weights (absolute and relative to body weight) are summarized in the following table.

% change in organ weight as compared to controls				
Organ	Day 91			
	Males		Females	
	Absolute	Relative	Absolute	Relative
Adrenal	---	---	↑28% H	↑73%
Heart	---	---	↓16% H	---
Kidney	↑25% M	↑21% M	↑19% H	↑58% H
Liver	↑10% L ↑19% M	---	↑30% H	↑73% H
Ovary	---	---	↓32% H	---
Spleen	↑24% L ↑35% M	↑24% L ↑37% M	---	↑56% H
Thymus	---	---	↓52% H	↓34% H
Day 506				
Adrenal	---	↑27%	---	---
Heart	---	↑23%	---	---
Kidney	↓19%	---	---	---
Liver	---	↑21%	---	---
Ovary			↓45%	↓37%
Pituitary	---	---	↓26%	---
Spleen	↓30%	↓11%	↓25%	↓20%
Thymus	↓28%	---	↑43%	↑59%

Histopathology: Adequate Battery: yes (X), no ()—explain

Peer review: yes (), no ()

The majority of the damage was observed in the HD animals' livers and kidneys. Renal tubular necrosis and glomerulonephritis were moderate to severe in the HD dogs and minimal in the MD dogs (males and females). Similarly, moderate to marked centrilobular necrosis and hepatocellular disassociation was observed in the livers of the HD dogs, while individual cell necrosis at minimal levels was noted in the MD dogs. Moderate to marked histiocytosis was seen in the lymph nodes, while slight to minimum lymphoid necrosis was seen in the Peyer's patches of the intestines and bone marrow. In the males, necrosis of the epididymis and seminiferous tubule degeneration were also noted. No ovarian damage was reported. Subacute vasculitis was reported in the lungs of the HD dogs.

At the end of the recovery period (15 months later), most damage had resolved or was at a slight to minimal severity. Glomerulosclerosis and renal tubule regeneration were seen in the kidney, while centrilobular fibrosis and pigmentation was observed in the liver. Histiocytosis was still observed in the lymph nodes. No microscopic correlate was noted for the enlarged prostates.

Toxicokinetics (Day 1, 28, 75, 90 at end of infusion, and 1, 4, 8, 12, 24 h after start of infusion) :

LISTING 10. MEAN DALBAVANCIN PHARMACOKINETIC PARAMETERS

GROUP	GENDER	STAT	DAY 1		DAY 28		CL (L/h)	DAY 90/77*		RECOVERY t1/2 (h)	
			Cmax (mg/L)	AUCt (h*mg/L)	Cmax (mg/L)	AUCss (h*mg/L)		Cmax (mg/L)	AUCss (h*mg/L)		
2	FEMALE	N	4	4	4	4	4	4	4	4	0
		MEAN	80.8	630.3	121.78	1424.5	0.0283	102	1109.5	0.0358	.
		S.D.	24.69	147.28	22.74	398.79	0.0059	15.09	177.74	0.002	.
		%CV	30.55	23.37	18.67	28	20.69	14.8	16.02	5.47	.
	MALE	N	4	4	4	4	4	4	4	4	0
		MEAN	82.34	672.79	117.88	1341.8	0.039	107.55	1237.5	0.0459	.
		S.D.	5.58	27.38	10.29	83.08	0.0066	26.2	207	0.011	.
		%CV	6.78	4.07	8.73	6.19	17	24.36	16.73	24.01	.
3	FEMALE	N	4	4	4	4	4	4	4	4	0
		MEAN	159.15	1353.9	221.42	2581.7	0.0311	207.28	2593.7	0.0324	.
		S.D.	11.42	144.47	27.76	301.4	0.0062	32.51	579.78	0.0061	.
		%CV	7.18	10.67	12.54	11.67	19.96	15.69	22.35	18.96	.
	MALE	N	4	4	4	4	4	4	4	4	0
		MEAN	151.25	1350.6	256.57	3182.1	0.0338	236.98	3192.7	0.0364	.
		S.D.	12.94	91.88	13.8	214.74	0.0034	33.01	464.89	0.0071	.
		%CV	8.55	6.8	5.38	6.75	10.17	13.93	14.56	19.54	.
4	FEMALE	N	4	4	4	4	4	4	4	4	3
		MEAN	667.42	6168.3	833.87	11714	0.0253	895.43	12008	0.0257	181.8
		S.D.	128.36	314.48	113.14	1119.3	0.0037	116.49	1179.1	0.0032	66.6
		%CV	19.23	5.1	13.57	9.55	14.53	13.01	9.82	12.36	36.66
	MALE*	N	4	4	4	4	4	4	4	4	5
		MEAN	608.51	5448.4	875.24	11719	0.0303	732.87	10573	0.0315	139.3
		S.D.	83.69	352.66	29.7	441.14	0.0032	61.35	792.67	0.0049	24.5
		%CV	13.75	6.47	3.39	3.76	10.53	8.37	7.5	15.59	17.59

* Indicates animals who entered the recovery phase of the study on Day 77. For these animals, the "Day 90" sample was taken on Day 75.

Comments and conclusions:

The study was adequate to determine the toxic potential of 3 months of daily administration of dalbavancin to dogs. The target organs of toxicity were primarily liver and kidney (necrosis), with lesser damage to male reproductive organs, lymphoid tissue (lymph nodes, Peyer’s patches in the intestine), and lung (vasculitis). Most of the damage resolved or diminished in severity with 15 months of recovery time. The NOEL for this study was 5 mg/kg.

3.4.4. Genetic toxicology: Reviewed previously in the initial submission and discussed above.

3.4.5. Carcinogenicity: Studies were not necessary as dalbavancin will be used for a short period of time.

3.4.6. Reproductive and developmental toxicology

Fertility and early embryonic development: This study was reviewed in a previous submission and is discussed above.

Embryofetal development

Study title: Embryo-fetal development study in CrI: CD(SD) BR rats of the test item BI397 administered by intravenous route at the dosages of 0, 5, 15, 45 mg/kg/day.

Report # (b) (4) 09070.

Conducting laboratory and location: (b) (4)

Date of study initiation: August, 2000

GLP compliance: Yes, OECD standards

QA reports: yes (X) no ()

Drug, lot #, and % purity: dalbavancin (BI397), Batch 024-B/R, 92.6% pure

Vehicle: 5% glucosate solution diluted 1:2 with water

Methods

Doses: 0, 5, 15, 45 mg/kg/day, intravenous

Species/strain: Cr;: CD (SD) BR rats

Number/sex/group: 25 females/dose

Route, formulation, volume, and infusion rate: intravenous, 5% glucosate diluted 1:2 with water, 5 mL/kg/day, 0.1 mL/sec; administered on days 6-17 of pregnancy

Satellite groups used for toxicokinetics:

Study design: standard

Parameters and endpoints evaluated: maternal clinical signs, body weights, and gross necropsy to include placentas, corpora lutea, feti; fetal weights, external/visceral skeletal anomalies.

Results:

Mortality (dams): All dams survived to scheduled sacrifice on GD20. No litters aborted.

Clinical signs (dams): There were no remarkable clinical signs with treatment.

Body weight (dams): There were no statistically significant differences in body weights or body weight gains between treated and control rats.

Food consumption (dams): Food consumption was decreased by 10-20% on GD 8 and 10 in the HD group as compared to controls.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

The pregnancy statistics based on both litter and individual fetus data are shown below. When counting litters only, the % with resorptions is higher at the HD. If evaluating the total # of feti resorbed, there is no dose response. There were no significant differences in the percentage of male or female feti.

Dose (mg/kg/day)	Gr# 1 0	Gr# 2 5	Gr# 3 15	Gr# 4 45	TREND (P)
Pregnant at term	23	23	19	17	
With early resorptions	9/23 39.13%	8/23 34.78%	10/19 52.63%	9/17 52.94%	>0.05
With late resorptions	0/23 0.00%	1/23 4.35%	1/19 5.26%	1/17 5.88%	>0.05
With resorptions	9/23 39.13%	9/23 39.13%	11/19 57.89%	10/17 58.82%	>0.05
With only resorptions	0/23 0.00%	0/23 0.00%	0/19 0.00%	0/17 0.00%	>0.05
With dead fetuses	1/23 4.35%	0/23 0.00%	0/19 0.00%	0/17 0.00%	>0.05
With only viable fetuses	13/23 56.52%	14/23 60.87%	8/19 42.11%	7/17 41.18%	>0.05

Dose (mg/kg/day)	Gr# 1 0	Gr# 2 5	Gr# 3 15	Gr# 4 45	TREND (P)
No. of females	23	23	19	17	
Corpora lutea	416	392	376	307	
Implantations	351/416 84.38%	338/392 86.22%	320/376 85.11%	272/307 88.60%	>0.05
Early resorptions	10/351 2.85%	10/338 2.96%	22/320 6.88%	11/272 4.04%	>0.05
Late resorptions	0/351 0.00%	1/338 0.30%	1/320 0.31%	2/272 0.74%	>0.05
Total no. of resorptions	10/351 2.85%	11/338 3.25%	23/320 7.19%	13/272 4.78%	>0.05
Dead fetuses	1/351 0.28%	0/338 0.00%	0/320 0.00%	0/272 0.00%	>0.05
Live fetuses	340/351 96.87%	327/338 96.75%	299/320 93.44%	260/272 95.59%	>0.05
Live male fetuses	159/240 66.25%	169/327 51.68%	152/299 50.84%	130/260 50.00%	>0.05
Live female fetuses	181/240 75.42%	158/327 48.32%	147/299 49.16%	130/260 50.00%	>0.05

Offspring (malformations, variations, etc.):

Fetal weights (in either males/females/overall) did not differ significantly with treatment. There were no significant differences in the number of feti with malformations with treatment. The number of skeletal anomalies increased in the HD group (28/170 in the control and 48/133 in the HD group), while there were anomalies in 15/22 control litters and 16/17 HD litters. The majority of these changes were

incomplete ossification of the cranium (frontals, interparietal, parietals, supraoccipital and nasals) and sternebra.

Comments and conclusions:

The NOAEL for the dams is 45 mg/kg. The NOAEL for the offspring is 15 mg/kg, with the major variations of incomplete ossification in the skull and sternebra. The dosing in the dams is not optimal in that there was no significant maternal toxicity. Body weight was not significantly decreased as compared to controls. The dose-ranging study was done at the same doses and did decrease maternal body weight by approximately 10% as compared to controls. Toxicokinetics were not collected in this study.

Prenatal and postnatal development

Study title: Intravenous Developmental and perinatal/postnatal reproduction toxicity study of dalbavancin (VER001) in rats, including a postnatal behavioral/functional evaluation. Study # 622-002.

Conducting laboratory and location: [REDACTED] (b) (4)

Date of study initiation: 2/24/03

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: dalbavancin, lot # 020004/R

Vehicle: 5% dextrose

Methods

Doses: 0, 5, 15, 30 mg/kg
Species/strain: Sprague Dawley Crl: CD(SD)IGS BR VAF/Plus pregnant female rats
Number/sex/group: 25 pregnant females/dose
Route, formulation, volume, and infusion rate: intravenous, 5 mL/kg at 10 mL/hr
Satellite groups used for toxicokinetics: 3 females/dose
Study design: daily administration on GD7 through day 20 of lactation (DL20)
Parameters and endpoints evaluated:

Results

F₀ in-life :

Mortality and clinical observations (twice daily): Two dams were sacrificed moribund on DL 9 and 12 due to tail damage (injection site). The main observation was damage to the injection site (tail) in 7/25 dams including green/purple/black discoloration, swelling, and tip of tail missing.

Body weight (daily during treatment, at sacrifice): There were no dose-dependent changes in body weight in that control and HD animals had similar body weights at both the end of gestation and the end of lactation. The LD and MD dams weighed more and gained more weight than control or HD (increased almost 2 fold during lactation, but

with a large variability). Maternal feed consumption was decreased in the HD dams by approximately 20% as compared to controls.

Necropsy (DL21): One HD female had 3 dead fetuses and placenta still present when sacrificed at DL2 following partial delivery. All other tissues appeared grossly normal.

Toxicokinetics (GD 20 at 1, 4, 8 24 h post-dose—maternal blood; DL 15 at 1-3 h post-dose—maternal milk; GD20 fetal blood samples; method = LC-MS/MS):

Maternal Plasma

	5 mg/kg/day	15 mg/kg/day	30 mg/kg/day
N	3	3	3
DG 20, 1 Hour Postdosage			
Dalbavancin (µg/mL)	53.040 ± 1.055	213.650 ± 6.944	366.333 ± 35.913 ^a
Metabolites (µg/mL)	BLOQ	BLOQ	BLOQ
DG 20, 4 Hours Postdosage			
Dalbavancin (µg/mL)	42.323 ± 2.772	138.473 ± 19.190	278.527 ± 3.966 ^a
Metabolites (µg/mL)	BLOQ	0.60 ± 0.00 [1]	BLOQ
DG 20, 8 Hours Postdosage			
Dalbavancin (µg/mL)	29.620 ± 4.773	102.677 ± 9.116	194.240 ± 34.787
Metabolites (µg/mL)	BLOQ	0.92 ± 0.00 [1]	BLOQ
DG 21, 24 Hours Postdosage			
Dalbavancin (µg/mL)	11.200 ± 2.939	28.947 ± 2.545	54.527 ± 6.558
Metabolites (µg/mL)	BLOQ	BLOQ	BLOQ

a. Estimated value; individual values were above the limit of quantitation.

[] = Number of values averaged.

BLOQ = Below the limit of quantitation.

Fetal Plasma

	5 mg/kg/day	15 mg/kg/day	30 mg/kg/day
N	3	3	3
Dalbavancin (µg/mL)	0.700 ± 0.000 [1]	7.12 ± 3.182	31.487 ± 12.580
Metabolites (µg/mL)	BLOQ	BLOQ	1.803 ± 0.677

[] = Number of values averaged.

BLOQ = Below the limit of quantitation.

Milk

	0 (Control Article) mg/kg/day	5 mg/kg/day	15 mg/kg/day	30 mg/kg/day
N	5	5	5	5
Dalbavancin (µg/mL)	BLOQ	5.568 ± 1.166	19.304 ± 1.909	35.410 ± 6.157
Metabolites (µg/mL)	BLOQ	BLOQ	BLOQ	BLOQ

BLOQ = Below the limit of quantitation.

F₀ necropsy:

In each dosage group, 23-24 of the dams were actually pregnant. There were no significant differences in the number of implantation sites, the duration of pregnancy. At the HD 16/24 litters had stillborn pups, as compared to 3 litters in the control group. A single dam at MD and HD had all pups die between days 1 and 4 of lactation.

F₁ physical development:

Viability and clinical observations (daily): Significantly more HD pups were stillborn as compared to controls. There were no significant differences in the ratios of males/females. Observations in the HD included 1 litter with an umbilical hernia, and 1 MD and HD litter each with head/back turned purple. After culling, there was also a slight increase in the number of animals with misaligned/broken incisors (0 control, 3/25 L, 4/25 M, 6/25 H males, 1/25 C, 1/25 L, 2/25 M, 3/25 H females. With the exception of the stillborn pups at the HD, the remaining findings were not toxicologically relevant.

Litter observations—F1 generation				
	Control	5 mg/kg	15 mg/kg	30 mg/kg
Total pups delivered (mean)	350 (14.6 ± 1.3)	345 (15.0 ± 2.2)	345 (15.0 ± 2.1)	294 (12.8 ± 2.8)
Liveborn	347 (99.1%)	333 (96.5%)	325 (94.2%)	236 (80.3)
Stillborn	3 (0.8%)	10 (2.9%)	9 (2.6%)	55 (18.7%)
Pups found dead/cannibalized D1	2 (0.6%)	1 (0.3%)	6 (1.8%)	3 (1.3)
Pups dead/cannibalized D2-7	4	4	2	9
Pup weight/litter, D1 (g)	6.4 ± 0.3	6.2 ± 0.4	6.0 ± 0.4	5.8 ± 0.5

Body weights (DL1, 4, 7, 14, 21): HD pups weighed less than control pups by approximately 10% on DL1. There were no significant differences thereafter through to mating in either gender.

Gross necropsy (DL21 for those not continuing):). There were no remarkable observations with treatment at necropsy. Testes and epididymis weights did not differ with treatment.

F₁ behavioral evaluation (passive avoidance, vaginal patency/preputial separation, auditory stimuli, water maze): There were no differences in time of preputial separation in males or vaginal patency in females between treated and control rats. Passive avoidance, auditory startle, and water maze parameters were not altered with treatment.

F₁ reproduction (25 rats/sex/dose):

Body weights (weekly; for females GD 0, 7, 10, 14, 17, 21): There were no significant differences in body weights, body weight gains, or food consumption in treated rats as compared to controls.

The fertility index was slightly decreased in the HD group: 21/24 rats mated in the HD group vs. 22/23 in the control group. All but 1 HD rat coupled in the first week

of mating. The number of pregnant rats decreased with dose: 22/23 control, 23/25 L, 20/23 M, and 21/25 H. None of these findings were statistically significant.

F₂ findings (implantation sites, resorptions, # live/dead fetuses, external and visceral malformations etc):

The number of corpora lutea, litter size, dead feti, resorptions, dams with viable fetu, and normal placentas did not differ significantly between treated and control, despite the fact that the number of implantations were significantly decreased in the HD as compared to controls (see table below). No significant differences in fetal weights were noted between treated and controls. There were no dose dependent, significant increases in malformations or variations in treated as compared to control litters.

PROTOCOL 622-002: INTRAVENOUS DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF DALBAVANCIN (VER 001) IN RATS, INCLUDING A POSTNATAL BEHAVIORAL/FUNCTIONAL EVALUATION

TABLE C24 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - F1 GENERATION FEMALE RATS

MATERNAL DOSAGE GROUP		I	II	III	IV	
MATERNAL DOSAGE (MG/KG/DAY)		0 (CONTROL ARTICLE)	5	15	30	
RATS TESTED		N	24a	25	24a	25
PREGNANT	N(%)	23(95.8)	25(100.0)	22(91.7)	22(88.0)	
DELIVERED AND SACRIFICED	N(%)	0(0.0)	1(4.0)	0(0.0)	0(0.0)	
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 21 OF GESTATION		N	23b	24b	22b	22
CORPORA LUTEA	MEAN±S.D.	18.0 ± 2.4	18.2 ± 2.6	18.4 ± 2.2	16.9 ± 2.4	
IMPLANTATIONS	MEAN±S.D.	16.6 ± 1.8	16.3 ± 1.7	16.5 ± 1.2	14.5 ± 3.5*	
LITTER SIZES	MEAN±S.D.	15.9 ± 2.1	15.4 ± 1.7	15.6 ± 1.8	14.2 ± 3.3	
LIVE FETUSES	N	365	371	343	312	
	MEAN±S.D.	15.9 ± 2.1	15.4 ± 1.7	15.6 ± 1.8	14.2 ± 3.3	
DEAD FETUSES	N	0	0	0	0	
RESORPTIONS	MEAN±S.D.	0.7 ± 0.8	0.8 ± 1.0	0.9 ± 1.2	0.3 ± 0.6	
EARLY RESORPTIONS	N	16	20	20	7	
	MEAN±S.D.	0.7 ± 0.8	0.8 ± 1.0	0.9 ± 1.2	0.3 ± 0.6	
LATE RESORPTIONS	N	0	0	0	0	
DAMS WITH ANY RESORPTIONS	N(%)	12(52.2)	12(50.0)	13(59.1)	6(27.3)	
DAMS WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	
DAMS WITH VIABLE FETUSES	N(%)	23(100.0)	24(100.0)	22(100.0)	22(100.0)	
PLACENTAE APPEARED NORMAL	N(%)	23(100.0)	24(100.0)	22(100.0)	22(100.0)	

a. Excludes values for rats that were found dead.
 b. Includes values for dams that did not have a confirmed mating date.
 * Significantly different from the control group value (p≤0.05).

Comments and Conclusions:

While significant maternal toxicity (other than to the injection site) was not seen, the study was adequate in that the highest dose did cause an increase in embryoletality. The maternal NOAEL was 15 mg/kg. The fetal NOAEL was 15 mg/kg. No teratogenic effects were seen, no effects on development, other than an increase in deaths during the first week of life (with no associated malformations or major decrements in weight), were observed. The fertility index and second generation feti were unaffected by the treatment to the F0 generation.

3.4.7 Local tolerance: These studies were reviewed in a previous submission and are discussed above.

3.4.8 Special toxicology studies**1. 622-010: Intravenous repeated dose 28-day immunotoxicity study of Dalbavancin (VER001) in rats.**

Conducting laboratory and location: [REDACTED] (b) (4)

Date of study initiation: November, 2003.

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: dalbavancin, lot # 2050-09-285048;

Formulation/vehicle: 5% dextrose

Positive control: cyclophosphamide (CYP), 50 mg/kg

Animals used: Sprague Dawley rats, 20/sex/group

Methods:

Doses: 0, 5, 10, 40 mg/kg/day for 28 consecutive days, intravenous (tail vein at lower doses, jugular catheters at 40 mg/kg/day).

Study design: Spleens from the treated and control rats will be analyzed for response to sheep RBC, splenocyte phenotypes, Natural Killer cell assay, and proliferative response to anti-CD3 mediated T-cell proliferation.

Results:

One male (5 mg/kg, Day 19) and 2 females (0 mg/kg, Day 13; 10 mg/kg, Day 11) were found dead. All deaths were shortly after removing from infusion restraints. The 5 mg/kg male and the 10 mg/kg female had dark/reddened areas on the lung.

At the 40 mg/kg/day dose in males, the tails were too swollen/discolored, missing by the end of 8 days and the animals were euthanized. Dosing was then done with a jugular (indwelling) catheter. Injection site swelling and discoloration was also seen in a dose dependent manner in the females. In the catheterized rats, dehydration was slightly more common in the 40 mg/kg males. Neurologic symptoms, such as hyperreactivity to sounds, head tilt, excessive salivation were noted in 1/20 animals.

Body weights were significantly decreased in the HD tail vein animals (approximately 10% decrease as compared to controls, roughly 50% decrement in body weight gain). A similar decrement in food consumption was observed. In the males

treated by catheter, body weight was decreased by approximately 15% at Day 29. Spleen weights did not differ significantly with treatment as compared to controls. However, with CYP treatment, spleens appeared small and were reduced by 50% or more. Splenocyte number was not reduced to a statistically significant extent in either males or females, while CYP decreased cell numbers by about 75%. T-cell subtypes, with the exception of NK cells at 40 mg/kg (decrements around 10%) were also not affected by dalbavancin, but diminished by >90% with CYP.

The sponsor concluded that immune function was minimally affected in dalbavancin treated rats over 1 month, with the NOEL for females at 40 mg/kg, and the NOEL for males at 10 mg/kg. I concur.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Dalbavancin is a lipoglycopeptide which interferes with bacterial cell wall formation and is active against Gram-positive bacteria. Early studies on the safety pharmacology of dalbavancin showed no effects on respiration, body temperature or behavior at doses up to 20 mg/kg in the mouse, rat, and or rabbit. Later toxicology studies at doses up to 80 mg/kg in the rat and 60 mg/kg in the dog showed, no clinical signs in the rat, while dogs at 40 to 60 mg/kg showed a histaminic response (ear congestion, mucosal pallor) with salivation.

As other compounds in the class have been shown positive in the hERG assay (see table below), a full preclinical cardiac work-up with dalbavancin was requested.

Class effects with glycopeptides					
Drug	Histamine response	HERG +	Δ BP	EKG	Human cardiac
Dalbavancin	Yes	NO	Yes * (↓)	No	NO
Oritivancin	Yes	Yes	Yes (↑)	No	No
Vancomycin	Yes	Yes	?	?	No
TD6424	Yes	Yes	No	Yes/No	?

*A decrement in BP was noted in some studies, but not all.

The hERG assay was negative; the maximum level feasible for testing was below plasma levels seen in the clinic. Similarly, the Purkinje fiber assay was negative, but the positive control did not show an effect. Blood pressure responses were variable: some studies showed a decrement during the first few hours (probably attributable to a histaminic response), while other studies did not. Anesthetized dogs did not show a change in blood pressure or ECG traces at doses up to 20 mg/kg nor did telemeterized dogs at doses up to 60 mg/kg. Finally, no evidence of QT interval prolongation has been noted in human clinical trials. In conclusion, dalbavancin does not appear to affect cardiac electrical function.

The pharmacokinetics of dalbavancin have been explored in mouse, rat, rabbit, dog, mini-pig and human. In most of the PK studies, the number of animals investigated is low (one or two/timepoint) so the values generated should be treated more like an estimation, not an absolute. Between the pharmacokinetic and toxicokinetic studies, there do not appear to be any gender effects on dalbavancin plasma levels. Given the long half-life and redistribution of dalbavancin, the collection period of data is critical.

Plasma half life, depending on how long the drug was followed in the plasma, was in the range of 1-3 weeks in rats and dogs. Tissue residence time in the dog was over 6 months. Dalbavancin was widely distributed into tissues, but did not cross the blood brain barrier. As there does not seem to be much of a contribution of metabolites to the plasma levels, method of detection should have a minimal impact on the final values (which was the case with the rat). Accumulation was seen, as one would expect, with multiple daily dosing in rat and dog. AUCs are roughly linear with dose. The AUC at the NOAEL in rat and dog ranges from approximately 1100 to 2200 ug.h/mL. Similarly, the range of AUCs at the lowest toxic level ranged from 2100 to 5100 ug.h/mL, a slight overlap. The human AUC to infinity (b) (4) following a 1000 mg i.v. dose then a week later by 500 mg i.v. is approximately 26000 mg.hr/L. At the lowest toxic level in rats and dogs, the AUC at the end of the treatment period is approximately 5-10 fold higher in humans than in dogs or rats. Excretion is via both urine and feces. The hydroxyl-dalbavancin metabolite is seen primarily in the urine.

The toxicologic profile of dalbavancin is similar in rats, dogs and humans. Injection site damage (necrosis, erythema, etc at the tail vein) was a dose-limiting toxicity in the rat in the 1 and 3 month intravenous studies. Both rats and dogs showed elevations of ALT/AST along with periodic alterations in cholesterol, protein and triglyceride plasma levels. The elevations in AST/ALT persisted in the dog for more than 15 months after the end of the treatment period, which is not unexpected given the long residence time of the compound in the liver. Microscopic damage included hepatocellular necrosis, vacuolization and degeneration. In the 3 month dog, damage was described as centrilobular necrosis and hepatocellular dissociation. In the kidney, elevations in BUN were seen in rat and dog which persisted through 15 months post-dosing in dog (slowly diminishing severity) and was demonstrated microscopically as tubular vacuolization/ degeneration/necrosis. In the 3 month dog, the severity of damage to the kidney was increased to mostly tubular necrosis, and glomerulonephritis was also observed. Pancreatic vacuolization/ degeneration/ apoptosis and acinar atrophy were noted with greater frequency in the rat. The relevance of this finding is toxicologically insignificant. No new toxicities arise with longer dosing periods, although some of the microscopic damage became more severe.

The clinical toxicities seen in the human trials have included gastrointestinal effects (nausea/vomiting/constipation/diarrhea), anemia, and liver enzyme elevations. Both rats and dogs appear predictive for the human, especially if the drug is administered by a catheter in the rat. The dosing schedule is such that the animals are exposed to a longer duration with daily dosing as opposed to the 2 dose (once weekly) schedule that humans receive.

The reproductive toxicity studies in rat and rabbit were adequate. The fertility index in the rat was decreased at 45 mg/kg/day, while the NOAEL was 15 mg/kg/day. No embryotoxic or embryo-lethal effects were seen in the Segment II study in the rabbit at doses up to 15 mg/kg/day during organogenesis. In the rat, the fetal NOAEL was 15 mg/kg/day with delayed ossification in the sternbrae and skull. In the segment III rat study, increased lethality (stillborn/unexplained early death in 1st week) was seen at the HD (30 mg/kg/day to the dams). No effects on developmental milestones or the F2 generation were observed. The NOAEL was 15 mg/kg/day. Dalbavancin levels in both

the pups' plasma and mothers' milk were approximately 1/10 of the maternal plasma levels of compound.

Dalbavancin was negative for mutagenicity and clastogenicity in the standard battery of assays. Dalbavancin was not irritating to skin or eyes and did not cause immunomodulation.

Conclusions: The exposure to dalbavancin is 5-10 fold less in the animals at toxic levels than the plasma levels seen clinically. The toxicities were similar in humans and the animal models (rat and dog). The main toxicities to injection site, kidney and liver are monitorable, although the changes in the liver and kidney persist for months after administration.

Unresolved toxicology issues (if any): The effects of dalbavancin, a compound with an extremely long residence time, are still being investigated in juvenile animals.

Recommendations: From the pharmacology/toxicology perspective, dalbavancin can be approved.

Suggested labeling:

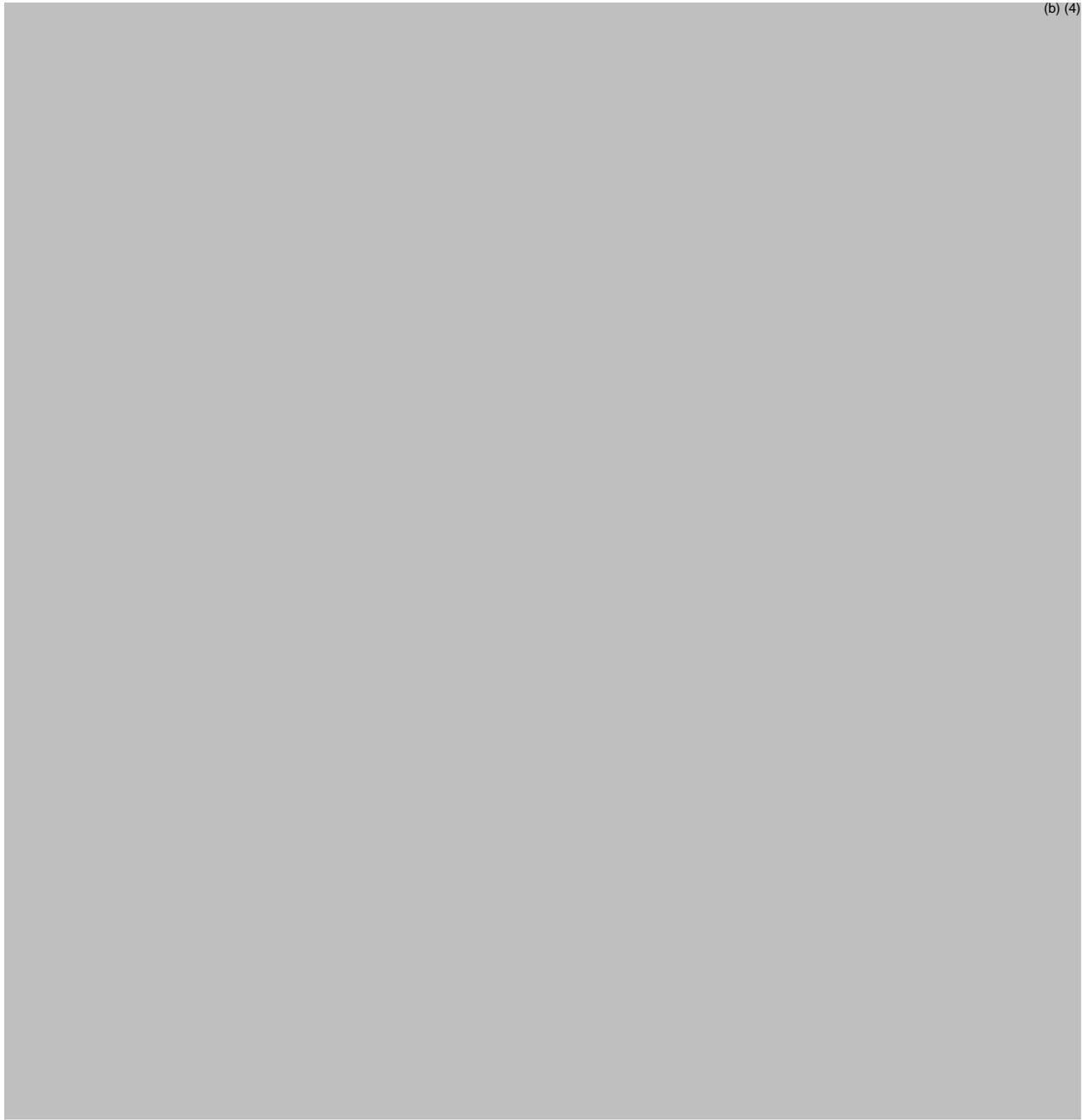
(b) (4)

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(b) (4)



Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

3.7. APPENDIX/ATTACHMENTS

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

/s/

Wendelyn Schmidt
8/18/2005 10:23:05 AM
PHARMACOLOGIST

Robert Osterberg
8/18/2005 11:12:27 AM
PHARMACOLOGIST

Lillian Gavrilovich
8/18/2005 02:04:45 PM
MEDICAL OFFICER