European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 5 December 2008
Doc. Ref: EMEA/CHMP/655741/2008

WITHDRAWAL ASSESSMENT REPORT

FOR

EXULETT

International Nonproprietary Name: **Dalbavancin**

Procedure No. EMEA/H/C/902

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu. http://www.emea.europa.eu

TABLE OF CONTENTS

I. RECOMMENDATION 4
II. EXECUTIVE SUMMARY 4
II.1 Problem statement 4
II.2 About the product 5
II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice 5
II.4 General comments on compliance with GMP, GLP, GCP 5
II.5 Type of application and other comments on the submitted dossier 6
III. SCIENTIFIC OVERVIEW AND DISCUSSION 6
III.1 Quality aspects 6
III.2 Non clinical aspects 7
III.3 Clinical aspects 16
IV. ORPHAN MEDICINAL PRODUCTS 59
V. BENEFIT RISK ASSESSMENT 59
V.1 Clinical context 59
V.2 Benefits 59
V.3 Risks 60
V.4 Balance 60
V.5 Conclusions 60

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
CI	Confidence Interval
CLSI	Clinical Laboratory Standards Institute (formerly NCCLS)
CoNS	Coagulase Negative Staphylococci
CRBSI	Catheter-related bloodstream infections
cSSTI	Complicated skin and soft tissue infection
EU	European Union
IDSA	Infectious Diseases Society of America
ITT	Intent to Treat
IV	Intravenous
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin Resistant *Staphylococcus aureus*
MRSE	Methicillin Resistant *Staphylococcus epidermidis*
MSSA	Methicillin Susceptible *Staphylococcus aureus*
NCCLS	National Committee for Clinical Laboratory Standards
NDA	New Drug Application
NNIS	National Nosocomial Infection Surveillance
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOS	Not Otherwise Specified
PCS	Potentially Clinically Significant
PCSC	Potentially Clinically Significant Change
PK	Pharmacokinetic
SAE	Serious Adverse Event
SOC	System Organ Class
SSI	Surgical Site Infection
SSTI	Skin Structure Tissue Infection
TME	Targeted Medical Event
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
uSSTI	Uncomplicated skin and soft tissue infection
VISA	Vancomycin-Intermediate Staphylococcus aureus
VRSA	Vancomycin-Resistant Staphylococcus aureus

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP consider that the application for Exulett in the treatment of ***Complicated skin and soft-tissue infections in adults when known or suspected to be caused by susceptible Gram positive bacteria***, is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Proposal for Questions to be posed to additional Experts

At this stage, no questions are proposed to be discussed by additional experts.

Inspection issues

The need for a GMP inspection of drug substance manufacturing sites is now identified. Inspections should be performed both by the same inspectors team in order to guarantee that both productions are equivalent. The results of the inspections should be available prior to the re-start of the timetable.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Bacterial infections of the skin and underlying soft tissues are one of the most common presentations in patients visiting emergency room clinics in both hospitals and office based practices. These can range in severity from uncomplicated skin and soft tissue infections (uSSTI), such as simple folliculitis, to life-threatening complicated SSTI (cSSTIs), such as necrotizing fasciitis. Complicated SSTIs involve deeper soft tissue and may require significant surgical intervention and parenteral antibiotic therapy (Fung, 2003). Within the hospital or long term care setting, cSSTIs are generally a consequence of surgery or regarded as a secondary infection associated with an underlying disease. Within the community, they are most often associated with the consequences of trauma.

Because of the great variation in seriousness and need of antibiotic treatment other interventions, diagnostic criteria and expected time to healing, it has been suggested that treatment of necrotizing fasciitis and burn wounds should be studied separately from other skin and soft tissue infections (European guidelines for clinical evaluation of anti-infective drug product 1993. European Society of Clinical Microbiology and Infectious Diseases). Abscesses needing immediate incision and drainage may also be unsuitable for testing the effect of antibiotic treatment as the surgical procedure may be sufficient alone (European guidelines for clinical evaluation of anti-infective drug product 1993. European Society of Clinical Microbiology and Infectious Diseases; Stevens DL & al., 2005; Gorwitz RJ, 2007; Ruhe JJ & al., 2007).

Even in studies where a significant number of the patients have complicating factors or co-morbidities that are thought to reduce the immune defence mechanisms against infections it has been found that cure for most of the patients is unrelated to effective antibiotic treatment (Gorwitz RJ, 2007; Ruhe JJ & al., 2007).

Studies on the effect of antibiotics therefore need to be well defined with documentation of both local and systemic signs of infection. Infections immediately treated with incision and drainage is less suitable for studies and one or more signs of systemic infections should be required (European guidelines for clinical evaluation of anti-infective drug product 1993. European Society of Clinical Microbiology and Infectious Diseases; Stevens DL & al., 2005). Furthermore, it is important that the type of infection is well characterized. The validity of the results requires also that a significant number of each type of infection is included and preferably separate analyses should be made if abscesses, burn wound infections and necrotizing fasciitis are included.

Although skin and soft tissue infections include a vast array of clinical entities, in their majority they are caused by two single microorganisms, *Staphylococcus aureus* and *Streptococcus pyogenes.* Antimicrobial surveillance studies (1997-2000) conducted in hospitalized patients across Europe, US, Canada, Latin America, South Africa, and Asia-Pacific regions found that *S. aureus* accounted for almost half of isolates from skin and skin structure infections (Bell et al, 2002; Diekema et al, 2001; Fluit et al, 2001b; Jones et al, 1999; Rennie et al, 2003). *Streptococcus pyogenes* has also been implicated in complicated SSTI, and to a lesser extent Group B beta-hemolytic streptococci (Fluit et al, 2001b; Stevens, 2004; Swartz, 2005).

In the setting of continuing emergence of resistance among Gram-positive pathogens worldwide, there is an increasing medical need for new antibacterial agents with enhanced Gram-positive activity. While *S. pyogenes* remains susceptible to penicillins, the emergence of resistance to all beta-lactam antibiotics in *S. aureus* raises a tremendous threat to public health. Glycopeptides such as vancomycin and teicoplanin were the only available options for treating most serious infections due to methicillin-resistant strains; however, concerns over increases in the rates of heteroresistance and tolerance to vancomycin, combined with its pharmacodynamic and clinical shortcomings and the increasingly important role of grampositive bacterial infections in the clinical setting, have motivated the development of newer agents. Dalbavancin, a lipoglycopeptide antibiotic, is a teicoplanin derivative that *in vitro* presents improved features respect to classical glycopeptides.

II.2 About the product

Dalbavancin is a second generation semi-synthetic lipoglycopeptide antibiotic structurally related to teicoplanin. Its mechanism of action involves the interruption of cell wall synthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits. This results in bacterial cell death. In *in vitro* studies, dalbavancin was active against Gram-positive bacteria. Its *in vitro* activity has been substantiated in various animal models of infection and it possesses a pharmacokinetic (PK) profile which allows once weekly intravenous dosing.

Dalbavancin is indicated for the treatment of complicated skin and soft tissue infections (cSSTIs) in adults, when known or suspected to be caused by susceptible Gram positive bacteria. The proposed posology is 1000 mg at day one, followed by a second dose of 500 mg 7 days later. Dalbavancin is administered intravenously over a 30 minute period.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

Dalbavancin was originally discovered by Biosearch Italia which merged with Versicor forming Vicuron. Vicuron was responsible for all clinical trials for dalbavancin, prior to their acquisition by Pfizer Ltd.

The applicant sought advice from regulatory authorities in the UK, Germany and Spain. Pfizer met with regulatory authorities in the UK and Germany (February 2006) and in Spain (April 2006), to discuss clinical issues relating to a submission for approval of dalbavancin for the treatment of complicated skin and skin structure infections in adults (see Pfizer Limited, 21 February 2006, Pfizer Limited, 23 February 2006 and Pfizer Limited April 2006, Module 5.4).

II.4 General comments on compliance with GMP, GLP, GCP

GMP: The need for a GMP inspection of drug substance manufacturing sites is now identified. Inspections should be performed both by the same inspectors team in order to guarantee that both productions are equivalent.

GLP: Pivotal, most of non-pivotal toxicity studies and safety pharmacology studies were GLP compliant.

GCP: The applicant states that all studies were conducted in accordance with the ICH Guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki, and that the designs of the Phase 3 studies were consistent with relevant regulatory guidance documents.

II.5 Type of application and other comments on the submitted dossier

Legal basis

Pfizer Limited applies for a marketing authorisation for the medicinal product dalbavancin 50 mg powder for solution for infusion according to art. 8(3) (full application) of a new active substance via centralised procedure, category art. 3(2)(a) "optional scope, new active substance".

Accelerated procedure

The Applicant has not requested accelerated assessment.

Conditional approval/exceptional circumstances

The Applicant has neither requested a conditional marketing authorisation nor an approval under exceptional circumstances.

Biosimilar application (N/A)

1 year data exclusivity (N/A)

1 year data exclusivity (N/A)

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Dalbavancin drug substance is considered a semi-synthetic cyclic lipoglycopeptide antibiotic consisting of two major families based on structural homology: **dalbavancin A** and **dalbavancin B**. **Dalbavancin A** family, which constitutes approximately 5% of the active drug substance, consists of two subtypes, designated as dalbavancin A_0 and A_1.
Dalbavancin B, which constitutes approximately 90 to 95% of the active drug substance, is comprised of the subtypes designated as dalbavancin B_0, B_1, and B_2.

There are several chemical modifications described that can suffice to consider dalbavancin as a chemical entity and then relevant guidance does apply.

Taking into account that different entities are involved, sufficient evidence of the quality of the batches from clinical trials to registration had been requested in the Day 120 List of Questions. The requested information was referred to fermentation particulars (any relevant incidence, strain used etc.) including purification steps linked to the corresponding A-40,926 lot (analytical results and method provided; manufacturing details such batch size and data). This intermediate is subsequently chemically modified (IPC controls) that leads to dalbavancin drug substance. Finally these drug substance lots are used to prepare drug product batches (through the corresponding manufacturing process that includes lyophilisation)

The information has not been provided in a suitable detailed format and therefore, because of this lack of information, there is not sufficient evidence to guarantee and support that former clinical and toxicological batches are representative of the current and future commercial batches.

In addition, some analytical issues linked to specification (and even to the levels toxicological sound) are still pending. Thus, these specifications might need revision.

Suitable specifications for both drug substance and drug product should be set.

The table of specifications should be updated.

Considering that the Applicant states that both fermentation processes are performed under GMP guidance, and because no sufficient detailed information has been provided, both intended sites should be inspected prior and as a condition for marketing authorisation.

Drug product

Evidence of similarity with regard to batches used for clinical trials and manufacturing procedure validation are still pending. Sufficient supportive information on IPC registration batches has also been requested.

Regarding the manufacturing procedure, the main steps such as sterilisation (bioburden limit and testing method etc.) have to be validated. In relation to lyophilisation some additional points have been recommended to be included in the validation protocol.

Some analytical and specification issues are still pending.
The table of specifications should be updated.
Label claim has been set clearly to 500mg. Assay results should be amended accordingly.

In the basis of some stability inconsistencies noticed, the proposed shelf life (36 month) can not be accepted

III.2 Non clinical aspects

Pharmacology

Non-clinical primary pharmacodynamic studies are included in Module 5, Section 5.3.5.3.1 (Microbiology Summary Report) and are not presented in Module 4.

Dalbavancin (test item) used for primary pharmacodynamic studies in vivo and mechanism of action studies in vitro is considered adequate. However, scant information was provided about the physical-chemical characteristics and composition of the test item used in those studies. The only information available is about its biological activity.

Dalbavancin pharmacology has been adequately characterized by the applicant. The study reports are generally detailed and of good quality, except for two studies of efficacy *in vivo*, which are referred as abstracts for conferences with low availability of data (Candiani 2001[1]; Heine 2005[2]). The studies provided explain that dalbavancin is an inhibitor of peptidoglycan (PG) biosynthesis with common mechanism of action with other glycopeptide antibiotics. At the effective dose for the inhibition of PG synthesis, syntheses of other macromolecules (DNA, RNA and proteins) are inhibited in a range between 15 and 40 %. However, it was not considered significant by the applicant. The studies performed to assess the potential for the emergence of resistance to dalbavancin showed that there is a low potential for emergence of resistance. Just enterococci and VRSA possessing the VanA- type

[1]Candiani GP, Romano G, Cavaleri M, et al. Efficacy of a Single Dalbavancin (DA) Dose Compared Multiple Linezolid (LN) Doses against Penicillin-Resistant Pneumococci (PRSP) in a Lobar Pneumonia (LP) Model in the Immunocompetent Rat (IR)". 41st Annual ICAAC. Chicago 2001.

[2] Heine HS, Bassett J, Miller L. In Vitro and In Vivo Activity of Dalbavancin (DAL) against *Bacillus anthracis (BA).* 45st Annual ICAAC. Washington DC 2005.

(genotype and phenotype) have shown reduced susceptibility or resistance to dalbavancin. However, data from similar studies on streptococci were requested to be presented. No emergence of resistance to dalbavancin was detected in animal infection experiments, or *in vitro* studies designed to detect development of resistance.

The *in vivo* testing program tried to corroborate the assumption that the in vitro activity of dalbavancin would translate to *in vivo* efficacy against infections caused by clinically important Gram-positive pathogens. In vivo studies employing various animal models of infection [soft-tissue (neutropenic murine thigh and granuloma pouch), deep-seated (rat and rabbit endocarditis), systemic (protection of mice from lethal infection), lung (murine pneumonia and inhalation anthrax model)] in which the primary endpoint was bacterial load in the infected site or tissue, showed the potential of dalbavancin to be efficacious against Gram-positive pathogens. For the prevention of acute septicaemia, dalbavancin was the most efficacious against *S. aureus* and *S. pyogenes*; showed similar efficacy to teicoplanin against *S. pneumoniae* and worst efficacy than teicoplanin against *E. faecalis*. For the treatment of endocarditis, dalbavancin showed the best activity profile against MRSA and *S. epidermidis* in rats. In the granuloma pouch model, 10 mg/kg dalbavancin (single dose) was as efficacious as other vancomycin or linezolid regimens against MRSA and MSSA respectively, but with a larger period prior to regrowth. Dalbavancin did not show protective effect from colonisation of medical devices. Effect of immune status on the activity of dalbavancin could only be evaluated in the pneumococcal pneumonia model in which had no effect. It could not be assessed in the acute septicaemia model because pathogens were different in the immunocompetent animals experiment from the neutropenic animals experiment. In this model, dalbavancin (10 mg/kg single dose) was also the most effective regimen tested in all parameters evaluated, both in immunocompetent and neutropenic rats and against PRSP or PSSP. All regimens of dalbavancin also showed preventive effect against B.anthracis administered 24 h after challenge. In general, dalbavancin single doses administered infrequently appeared to be more effective than frequent administration of smaller doses.

No secondary pharmacodynamics studies have been provided. It was justified by the applicant due to the bacteria-specificity of the target (peptidoglycan), and also supported by the lack of effects in the safety pharmacology studies. The applicant did not consider necessary to test dalbavancin in a broad ligand receptor screen. This view was not supported. Dalbavancin agonistic or antagonistic effects on other therapeutic targets (for example receptors) cannot be excluded and a receptor screen was considered to be performed. This concern has not been solved yet.

The safety pharmacology evaluation included the assessment of potential effects of Dalbavancin on Central and Autonomic Nervous Systems, Respiratory System and Cardiovascular System including coagulation components.

Intravenous administration of single doses of dalbavancin up to 20 mg/kg did not result in any statistically significant effect on CNS (neurobehavioral parameters or body temperature) in mice or on Autonomic Nervous System (cardiac baroreflex response) or Respiratory System parameters evaluated in rats.

Cardiovascular effects were evaluated in 2 *in vitro* studies and in several *in vivo* studies including 4 studies in telemetered conscious dogs.
In the *in vitro* action potential duration (APD) assay using rabbit Purkinje fibers, dalbavancin up to 16.8 µg/ml (near the maximal soluble concentration of 20 µg/ml) appeared to increase the action potential (AP) duration although effects were not considered significant. Similarly, non significant effects were observed on action potential amplitude, maximum upstroke velocity or resting membrane potential.

In the hERG ion channel blockage (for IKr), dalbavancin at 16.9 µg/ml (actual concentration 15.5 µg/ml) produced no inhibition of hERG current. IC_{50} for inhibitory effect could not be determined since the assay was performed at the limit of dalbavancin's solubility.
The highest concentrations used in both *in vitro* studies were slightly lower to the expected free concentration of dalbavancin in human plasma at Cmax.

In two of the *in vivo* studies by telemetry, dogs received doses of 30, 40, or 60 mg/kg of dalbavancin over a 30-minute infusion period in dosing sessions separated by 1 week. Arterial blood pressure and heart rate were evaluated. In one study, a twenty-second ECG tracings were registered and concentrations of dalbavancin were determined. There were no abnormal electrocardiograph arrhythmias, conduction disturbances, or quantitative abnormalities (including QT or QTc interval prolongation). Mean Cmax of the 60 mg/kg dose session was ~4-6-fold the clinical Cmax. Mean cumulative exposure (total AUC across all three administered doses) was over 3-fold that for the clinical dose. Furthermore, no abnormal ECG findings were observed in the 3 month toxicity study in dogs using dalbavancin doses up to 40 mg/kg/day, corresponding to a plasma dalbavancin concentration 4.7 times the level observed in clinical studies.

Low magnitude decreases in blood pressure and increases in heart rate that occasionally were statistically significant were intermittently observed during and/or after infusion (30 minutes of infusion period). These effects were accompanied by cutaneous swelling and/or erythema, particularly of the face and paws and were noted from mid-infusion to approximately 1 hour after the end of the infusion. All these effects were attributed to histamine release. Infusion reactions were observed in all toxicology studies in dogs where the infusion period was ≤11 minutes and in safety pharmacology studies in dogs where the infused dose was ≥30 mg/kg. These suggested that effects were related to a combination of the dose solution concentration and the rate of infusion.

In an *in vitro* study using rabbit platelets, dalbavancin inhibited collagen-induced platelet aggregation. A 10^{-4} M dose of dalbavancin induced a statistically significant inhibition. The calculated IC_{50} was 2.72×10^{-4} M (494 µg/ml). Maximal effect was obtained at 10^{-3} M (~ 1800 µg/ml). This observation is however not confirmed in rat *in vivo* at dalbavancin doses up to 20 mg/kg.

The applicant considered the study of pharmacodynamic drug interactions was not applicable. The applicant's view was not supported and a question on this issue was raised in the Day 120 List of Questions.

In vitro interactions of dalbavancin with other antimicrobial agents were studied. Dalbavancin synergistic interaction with oxacillin was observed against staphylococci and 2 susceptible vancomycin-susceptible *E. faecalis*. No antagonistic interactions were observed. However, it was considered to deeply investigate the potential for in vitro synergistic/antagonistic interactions with class representative agents normally prescribed for mixed-infections caused by Gram-positive and Gram-negative bacteria; it was just studied for aztreonam. At least it should have been justified the selection of this agent as representative for the target group of anti-infective agents under study. There were also available data about gentamicin and levofloxacin (active against some Gram-negative bacteria) in the second study, though they are not reported as anti-Gram-negative agents. There were not observed antagonistic or synergistic interactions between dalbavancin and these two antibiotics. However, at in the Day 120 List of Questions the applicant was requested to provide more data on potential in vitro synergistic/antagonistic interactions of dalbavancin with class representative agents indicated for mixed-infections caused by Gram-positive and Gram-negative bacteria; it had just been studied for aztreonam. The Applicant has submitted in the Responses Document a new drug-drug interaction study comprising dalbavancin and 10 commonly prescribed anti-Gram negative agents, revealing no antagonistic or synergistic effect on either of the antibiotics tested.

Potential interactions between dalbavancin and other non-antibacterial agents were not studied.
The Applicant was requested to provide a more detailed discussion on this topic, taking into consideration comedication with drugs relevant for the actual patient population. This concern related to the lack of secondary pharmacodynamics studies and pharmacodynamic drug interaction studies with non-antibacterial agents has not been solved yet. However, the applicant as requested in the Day 120 List of Questions, has submitted dalbavancin to Cerep S.A. for a broad receptor screen assay (BioPrint® profile), but the final report is not available yet.

Pharmacokinetics

Pharmacokinetic (PK) studies have been performed *in vitro*, and *in vivo* using both unlabelled and radiolabelled dalbavancin. PK-data have been collected in rats, dogs and rabbits, the species used in general toxicology studies. Dalbavancin and metabolites have mainly been analysed using LC/MS-MS methods. Radioactivity contents in samples have been analysed by liquid scintillation counting (LSC) and liquid chromatography with radiochemical detection (LC/RC), for tissues and carcasses radioactivity in $^{14}CO_2$ resulting from complete combustion has been counted. A HPLC method was used for detection of dalbavancin and metabolites (metabolite profiling) in plasma, urine, and faeces from rats and dogs.

The LC-MS/MS method is considered acceptable. For LSC and LC/RC used in studies were animals were given radiolabelled dalbavancin, and the HPLC method used for metabolic profiling, no reports on the methods could be located in the dossier and the applicant was requested to provide such reports. The issue has been solved.

In SD rats and Beagle dogs, PK parameters were comparable in males and females. Exposure levels after administration of dalbavancin intravenously (iv) increased in a roughly dose-dependent manner. In repeat-dose toxicity studies, animals were dosed every day and steady state levels were established within 1 month. Any accumulation on Cmax and AUCs observed at week-4 compared to levels on Day 1 was less than 2-fold. Plasma half-life (t½) of dalbavancin is long and increase with elapsed time between last dose and last observed plasma concentration, supporting a polyexponential disposition. In rats given a single dose (20 mg/kg) and followed for 120 days, the predominant t½ was 14 hours and the terminal t½ 630 hours. In dogs administered a single dose of 20 mg/kg and followed for 118 days, the predominant t½ was 24 hours and the terminal t½ was 646 hours. In humans a triphasic plasma elimination of dalbavancin is reported. Mean t½ in healthy subjects receiving a regimen of 1000 mg (day 1) plus 500 mg (day 8) dalbavancin was 321 hours (study 001-12). The applicant was requested to discuss mechanisms contributing to the extensive t½ for dalbavancin and it is considered adequately clarified.

There is a high degree of tissue distribution in rats and dogs and elimination is rather slow.
In rats, radiolabelled dalbavancin distributed to all tested tissues/organs. Collectively tissues contained 31.51% of administered radioactivity after 7 days, the tissue with the greatest amount of radioactivity was the skin (7.06% of the dose), followed by liver (4.20%), and kidneys (2.51%). Low but detectable concentrations of drug-derived radioactivity were found in the CNS. Radioactivity in tissues declined gradually and after 120 days only the carcass retained more than 1% of the initial dose (1.76%). Collectively the tissues from rats contained 2.49% of the dose on day 120. All examined tissues in rats showed a t½ of more than 12 days.
In dogs, dalbavancin also distributed to all examined tissues. Similar to rats, the level of radioactivity in tissues/organs was reduced over time, from 15.7% on day 70 to 7.2% on day 181 for tissues collectively. However, dogs retained a much higher level of dalbavancin related radioactivity in liver than rats. The level was significant even after 181 days (6.2% of administered dose). At this time point all other tissues retained less than 1%. In both rat and dog, radioactivity in liver was mainly present in hepatocytes. The applicant was requested to suggest possible mechanisms for the noticeable retention of dalbavancin in dog liver and discuss the potential clinical relevance, taking into consideration that liver is one of the target organs for toxicity in animals. This issue has been adequately addressed in the Document of Responses to the Day 120 List of Questions.

Volumes of distribution at steady state (Vss) were 0.18 to 0.33 L/kg in mice, 0.14 to 0.38 L/kg in rats, 0.12 L/kg in rabbits, and 0.3 L/kg in mini-pigs. Volume of distribution after a single dose in dogs was 0.14 L/kg. Plasma clearance scale allometrically by species body weight. Across all species studied, dalbavancin had low plasma CL. In mice, rats, rabbits, dogs, and humans, CL increased with increasing animal size and it was directly related to species body weight.

Dalbavancin crosses the placenta and is excreted in milk in rats. Concentrations in foetal plasma as well as milk increase with the maternal dose. At a maternal dose level of 30 mg/kg/day, dalbavancin concentrations in foetal plasma and milk are more than 50% of the concentration in maternal plasma.

Based on results from these animal studies it can be assumed that dalbavancin will be excreted in human breast milk. Although absorption from the infants' gastrointestinal tract probably is low, the risk of influence on the child intestine- and mouth flora cannot be excluded.

Binding of dalbavancin to plasma proteins is shown to be 93-94% in rat, dog, and man. Furthermore, in blood dalbavancin appears to be in plasma rather than associated with cellular components of blood.

In an *in vitro* study, mouse macrophages in a solution of dalbavancin had cell-associated concentrations of drug that exceeded that in the surrounding solution by factors between 5.9 and 25.5. *In vitro*, dalbavancin was neither metabolized by hepatic microsomes nor by hepatocytes from rat, dog, and human. In addition, dalbavancin was not metabolized by human kidney microsomes and dalbavancin showed no inhibition of the activity of individual cytochrome P450 isoenzymes (CYP1A2, CYP2A6, CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP2E1). In an *in vivo* study dalbavancin did not have any clinically relevant induction effects on P450 isoenzymes (1A2, 2A1, 2B1, 2C, 2C6, 2D2, 2E1, 3A1) activity.

Metabolism of dalbavancin appears to be similar in rat, dog and man. Two metabolites have been identified, OH-dalbavancin and mannosylaglycone (MAG). Unchanged dalbavancin is the major component in plasma and faeces, while 10-23% OH-dalbavancin and 5% MAG is detected in urine of rat and dog. In humans, metabolic profiling of plasma and urine gave similar results as in animals, samples of faeces have not been examined for metabolites. In view of the results from *in vitro* studies indicating that dalbavancin does not undergo biotransformation in liver or kidneys, it is unclear how OH-dalbavancin is formed. The applicant was requested to provide a more detailed discussion on this issue and suggest possible metabolic pathways. It was also remarkable that the metabolites OH-dalbavancin and MAG are detected in urine and faeces, when the levels in plasma were claimed to be negligible. The applicant has provided a plausible reasoning for this finding and the question is considered as solved.

Metabolism of dalbavancin has not been examined in rabbit. Since rabbit has been used for testing of potential toxicity to embryofoetal development, this is deficient.

Dalbavancin is excreted via urine and faces in rat and dog. 42-65% of dalbavancin related material is recovered in urine and 9-26% in faeces (over 120-181 days). Similar data are obtained in humans. Although recovery appears to increase with time, complete recovery is not achieved in any species. In animals, radioactivity in tissues and cage rinse is included in total recovery. It was therefore unclear why not more than 80-90% of the administered radioactivity has been accounted for throughout the studies. The applicant was requested to discuss possible explanations. Adequate discussion has been provided for this finding in the Applicant's Response Document.

Pharmacokinetic drug interaction studies have not been conducted. The need for such studies was requested to be reconsidered by the applicant, in relation to the discussion on the potential metabolic pathways. In addition, the absence of any study on transporter based interactions was requested to be justified, given their significant role on the distribution and elimination of co-administered drugs. The issue has been adequately addressed by the Applicant.

Toxicology

The toxicological profile of dalbavancin was evaluated in standard toxicology studies. Mice, rats, dogs, rabbits and guinea pigs were used.

The oral and IV acute toxicity of dalbavancin was evaluated in rats and mice. The oral LD_{50} was greater than 2000 mg/kg in both rat and mouse. Adverse clinical signs occurred only in the IV mouse and rat studies at dose levels where mortality also occurred. These signs included transient shallow breathing at ≥186 mg/kg and sedation, hypoactivity, and piloerection starting immediately after dosing in the 200 mg/kg and higher doses. Clonic convulsions occurred at 225 mg/kg and higher. Mortality

occurred at all IV dose levels ≥186 mg/kg. The IV LD_{50} for both mice and rats was calculated to be ~ 200 mg/kg.

Several non-pivotal GLP, 4-week repeated-dose toxicity studies including TK assessment were performed in rats and dogs by IV route at doses up to 80mg/kg and 60 mg/kg dalbavancin, respectively.

Pivotal repeated-dose toxicity studies were conducted in rats and dogs up to 3 months by IV route. An interim necropsy at 28 days was included in the rat study while only clinical pathology determinations were performed at 28 days in the dogs study. In rats the highest daily dose tested was 10 mg/kg (up to 3 months) or 40 mg/kg (up to 1 month) corresponding to 1.1-fold and ~3-fold human therapeutic exposure based on cumulative AUC over 14 day (14-days AUCcum), respectively. In dogs the highest daily dose tested was 40 mg/kg corresponding to ~6-fold human therapeutic exposure based on 14-days AUCcum.

Dalbavancin induces similar systemic toxicity in both rats and dogs. Main target organs for toxicity in animals are kidneys, liver, and red blood cells.

The renal toxicity observed was dose-dependent and evident at ≥20 mg/kg in 4-week non-pivotal studies and at ≥10 mg/kg in 3-months studies. It was characterised by increased blood urea nitrogen and creatinine levels, and findings of blood and epithelial cells in urine. Furthermore, histopathological evidence of tubular toxicity; including dilatation, degeneration and necrosis of epithelial cells associated with regenerative basophilia, interstitial inflammation, and pigments in histiocytes was observed. Kidneys were pale and their weight was increased. Renal toxicity was generally more severe in dogs than in rats. After recovery, increased kidney weights were still present in rats and increased blood urea nitrogen and creatinine, glomerulosclerosis and tubular degeneration were observed in dogs (up to 15 months recovery). The NOAEL for kidney was 10 mg/kg for 4 weeks of dosing (0.7-1.6-fold human therapeutic exposure) and 5 mg/kg for 3-months of dosing (~0.6 –fold human therapeutic exposure).

The Applicant was asked for an adequate discussion on the mechanisms and potential clinical relevance of renal toxicity observed in animals; taking into consideration that renal toxicity was severe and partly irreversible in rats and dogs, the long half-life of dalbavancin, and the narrow or unidentifiable safety margins (0.6 to 1.6-fold the human therapeutic exposure). The issue has been solved from the non-clinical point of view.

Hepatotoxicity was also dose-dependent and evident at ≥40 mg/kg in 4-week studies and at ≥10 mg/kg in 3-months studies in rats and dogs. The NOAEL for liver was proposed at 20 mg/kg for 4 weeks of dosing (~ 1.8 to 2.6- human therapeutic exposure) and was 5 mg/kg for 3-month of-dosing (~0.6 –fold human therapeutic exposure). Liver toxicity was characterized by clinical chemistry changes (significantly increased AST and ALT) and by histologic effects. Increased cholesterol and triglyceride or decreases in albumin levels were also noted. Transaminase elevations were observed earlier than histologic or other changes (pale liver, increased liver weight) and persisted after histologic findings had reversed. In the 3-month studies, total bilirrubin and GGT were also increased in dogs.
Dose-dependent hepatocellular centrilobular necrosis was observed in dogs dosed at ≥10 mg/kg for longer than 2 months. Was reversible, but residual hepatic fibrosis was present after administration of higher doses (dogs) and clinical chemistry parameters remained elevated even after a recovery period up to 15 months (7-9-fold for transaminases).

The applicant was asked for an adequate discussion of the mechanisms and potential clinical relevance of the hepatotoxic effects; taking into consideration that hepatic changes were severe and partly irreversible in both rats and dogs, and the narrow or unidentifiable safety margins (1.8 to 2.6-fold the human therapeutic exposure in the 4-week study and ~0.6 –fold the human therapeutic exposure in the 3-month study). Also, considering the long half-life of dalbavancin, the Applicant was requested to discuss whether or not monitoring of patients could be necessary taking into account that possibly the

clinical hepatotoxic risk may increase if patients would be treated for longer periods or repeatedly. Furthermore, as patients are exposed to dalbavancin for a rather long period of time after cessation of treatment, the Applicant was requested to discuss how to manage liver toxicity clinically if this occurs. According to the data available, hepatobiliary events should be monitored as a potential risk.

Several signs of haematological toxicity were observed in the repeated-dose toxicity studies in dogs and less consistently in studies in rats (reduced RBC, haemoglobin, hematocrit and increased number of platelets in rats or decreased in dogs). In the 3-month toxicity study in dogs values for these erythroid parameters reversed into baseline after several months of cessation of the treatment. The nonclinical overview does not include a discussion on the potential consequences of these effects on patients. The applicant was requested to submit discussion of possible mechanisms and the potential clinical relevance of these findings. According to the discussion provided, the safety profile of dalbavancin with respect to adverse events potentially related to haematological parameters seems similar to or better than the comparators, mainly linezolid.

Epididymal necrosis and diffuse seminiferous epithelial degeneration was observed in the 3-month study in dogs dosed for 77 days at 40 mg/kg. Degeneration of seminiferous tubules was also observed in 1 out 4 males at 10 mg/kg treated for 3-months. This latest finding did not completely reverse after recovery (see also Fertility and early embryonic development below).

Vacuoles and/or dark pigment were observed in the cytoplasm of parenchymal cells in a variety of tissues (hepatocytes and renal tubular epithelium, mammary gland, pancreatic acinar epithelium, lymph nodes, adrenal glands, heart, lung, spleen, and thymus) and in macrophages from several tissues. In some cases, dark pigments showed positive staining for hemosiderin, suggesting relation to decreased red blood cell parameters. These findings were dose-dependent in incidence (number of affected animals) and extent (number of affected tissues). According to the applicant, vacuoles and/or dark pigment are not considered adverse, ie, they were not considered to be evidence of toxicity, because there was no correlation to cellular damage or organ dysfunction and their presence is interpreted as evidence of increased cell membrane turnover with accumulation of lipofuscin ('wear and tear') pigment. These findings diminished in incidence but not completely reversed after recovery. Nevertheless, the Applicant was requested to discuss possible mechanisms for this effect and potential clinical relevance. The potential effects of dalbavancin on macrophage function activity have been addressed in the Immunotoxicity section included below.
Regarding the possibility of dalbavancin effect on endocrine pancreas, detailed information was requested to be provided considering some results such as islet hyperplasia sporadically observed, taking into account that no accurate morphological study using electronic microscopy investigation has been conducted and no discussion is included in the overview. Therefore, the applicant was requested to reassure that dalbavancin has no physiological implication in glucose homeostasis. Although a discussion is provided from a non-clinical point of view, it should be considered that altered glucose homeostasis has been seen in patients receiving dalbavancin in phase 3 trials. No mechanism for hypo- or hyperglycaemia has been demonstrated for this class of medicinal product.

Intravenous administration of dalbavancin was associated with immediate infusion reactions in dogs, characterised by facial/and or paw swelling, salivation, vomiting, hypotension and increased heart rate. The effects were transient and most likely related to histamine release. Furthermore, repeated intravenous injections resulted in local reactions at the injection site in both rats and dogs. The severity of the effects appeared to be related to both dose and administration frequency and resulted sometimes in dose-limiting reactions characterised by inflammation, necrosis, haemorrhage, thrombosis, as well as fibrosis. In general these toxic effects were reversible.

Dalbavancin was evaluated in a battery of Genotoxicity assays that included *in vitro* mammalian cell assays for gene mutation and cytogenetic evaluation of chromosomal damage plus an *in vivo* mouse micronucleus assay. According to results dalbavancin seems to have no genotoxic potential.
The Applicant did not justify the lack of a bacterial reverse mutation test. It is well known that this test may not be appropriate for some antibiotics, however as dalbavancin is active against Gram-positive bacteria and strain use in the AMES assay are Gram-negative it is not clear why the AMES-assay

should not be appropriate. In addition, the ICH S2B guideline recommends in part 4.1 that "it is still important to perform the bacterial reverse mutation test (some antibacterial agents, albeit highly toxic to tester strains, are detected as genotoxic at very low, sub-lethal concentrations in the bacterial reverse mutation test); either a full test or a limited (range-finding) test may be appropriate". The applicant should provide a relevant justification for omitting the test. In the gene mutation test in mammalian cells (RBM971099), no significant cytotoxic effects were observed at any dalbavancin concentration tested (up to 2000 µg/ml). According to the ICH guideline, a certain level of cell toxicity is desired in order to allow adequate evaluation of negative test results. However, due to limited solubility of dalbavancin, it is accepted that 2000 µg/ml was the highest feasible concentration. Finally, the applicant did not show any data on dalbavancin exposure in the *in vivo* study in CD1 mice (RBM990751). Furthermore, neither data on pharmacokinetic, nor on metabolism from mice for the applied dose range is available in other parts of the dossier. The applicant was requested to provide data to show that bone marrow cells in animals were exposed to clinically relevant levels of dalbavancin metabolites. Alternatively, the Applicant was requested to discuss the need for separate testing of the metabolites OH-dalbavancin and MAG for genetic toxicity.
All these issues have been solved in the Applicant's Response Document.
No carcinogenicity studies have been submitted. According to the applicant carcinogenicity studies were not conducted as the intended duration of dalbavancin clinical use is less than 3 months, dalbavancin is not indicated for a chronic, recurrent condition, and there was no signal of genotoxicity with dalbavancin, no class effect of lipoglycopeptide antibiotics suggesting a carcinogenic risk, no structural alerts in any of the dalbavancin components or metabolites suggesting a risk of carcinogenesis, and no evidence in toxicology studies of preneoplastic findings or tissue changes attributed to drug residence time. The justification for omitting long term carcinogenicity studies is considered acceptable.

Fertility and early embryonic development were studied in male and female rats dosed with IV dalbavancin up to 45 mg/kg. At this dose level, general toxic effects were observed in males (mortality, clinical signs, reduced body weights, body weight gains, food consumption, and nephrotoxicity) and in females (reduced body weight gain and food consumption). The NOAEL of dalbavancin for general toxic effects on F0 males and females was determined to be 15 mg/kg/day.
A dose of 45 mg/kg/day (3.5 times the human dose on exposure basis) caused a statistically significant reduction in fertility index (from 96% in controls to 58% at 45 mg/kg/day) an increase in the average number of resorptions and a slightly reduction in testes weight. Microscopically prostate and seminal vesicles showed slight to moderate glandular atrophy (9/23, 5/23, slight, moderate respectively) and a decreased content of secretory material (8/23, 8/23, slight, moderate, respectively). No sperm analysis was performed at any dose level. In females, oestrous cycling was unaffected by doses up to 45 mg/kg/day.
The reasons for the decrease in fertility including fertility index were not clarified and elements of discussion were not provided. On the whole, the effects of dalbavancin on male fertility (including functional effects) were not sufficiently addressed. As showed in the whole body autorradiography Study RBM090208 in rats, intense exposure was observed in testes up to 120 h post treatment with a single ^{3}H-dalbavancin dose at 20 mg/kg. In addition, epididymal necrosis and diffuse seminiferous epithelial degeneration was observed in the 3-month study in dogs (Redfield Study 168-003) after 77 days of treatment. Degeneration of seminiferous tubules did not completely reverse. The applicant was asked to provide a more in depth discussion regarding potential effects of dalbavancin on fertility. The NOAEL for mating and fertility was determined to be 15 mg/kg/day.

Effects on embryo-foetal development of dalbavancin administered IV were evaluated in rats and rabbits. In rats dalbavancin at doses of 5, 15 and 45 mg/kg/day induced at 45 mg/kg/day some materno-toxic effects (lower body weight gain and food consumption) during the treatment period, mostly related to a decrease in body weight gain during the first two days of treatment. At 15 mg/kg/day the slight effect on body weight gain and food consumption was not statistically significant.
A statistically significant increase in skeletal anomalies (mostly related to reduced ossification of cranial bones) and skeletal variants observed in foetus from dams treated at 45 mg/kg/day was

considered a delayed in foetal maturation and related to the slightly lower mean foetal weight present in this group. NOAELs for F0 dams and for F1 foetuses was set at 15 mg/kg/day.

Toxicokinetic data are missing from fertility and early embryonic and embryo-foetal development studies, but based on pharmacokinetic data from a different rat study, exposure levels in rats at NOAEL are estimated to be similar to the therapeutic exposure level in humans.

In rabbits, a dose of 15 mg/kg/day caused abortion in 2 out 22 pregnant females (DG 20 and 21) and a reduction in body weight gain and food consumption. The maternal NOAEL was 5 mg/kg/day and the developmental F1 NOAEL set by the applicant at 15 mg/kg/day (based on non drug-related external, soft tissue or skeletal alterations) has been revised and has been set at 5 mg/kg/day (to take into account abortions observed at 15 mg/kg/day). No toxicokinetic data have been collected from rabbits after repeated dosing and metabolism has not been examined. It was therefore impossible to evaluate the clinical relevance of using rabbit as a model. The applicant was requested to provide relevant data to support the choice of rabbit as the non-rodent species, and to allow calculation of safety margins. This has been adequately addressed by the Applicant.

In a rat peri-natal and post-natal development study, IV doses at 30 mg/kg/day of dalbavancin caused irritation at the injection site and reductions in food consumption at the beginning of the gestation and throughout the lactation period. The maternal NOAEL was 15 mg/kg/day.
The 30 mg/kg/day dosage was associated with apparent dystocia or prolonged gestation (2 out 25 dams) and caused increased numbers of stillbirths, increased pup mortality (Days 2 to 4 postpartum) and reduced pup body weight (on Day 1 postpartum). The reproductive NOAEL in dams and litters at delivery was also 15 mg/kg/day. Measures of growth and viability of litters were comparable among groups for the remainder pre- and post-weaning periods. The NOAEL for viability and growth in the offspring was 30 mg/kg/day.
Toxicokinetic data from F0 animals revealed a C_{max} at NOAEL slightly lower than what is observed in humans at therapeutic exposure. Furthermore, dalbavancin was detected in foetal plasma, and was excreted in rat milk. OH-dalbavancin in foetal plasma was below the limit of quantification.

For local tolerance assessment, a single perivenous (subcutaneous) and intravenous injection study was performed in rabbits using dalbavancin at 10 mg/ml concentration in the dosing solution (2 lots corresponding to 2 formulations). The highest final concentration for injection in the clinical use (after reconstitution and dilution) is 3.3 mg/ml. Although it is recommended that the actual concentration of active substance to be used in humans be tested in animals, it was showed that dalbavancin by IV route was non irritating. Results in the perivenous study showed that oedema and erythema were present for up to 4 days postinjection with histologic mild inflammation. Therefore, extravasation could be irritating to tissues in the clinical use.

Dalbavancin was not considered a dermal or eye irritant to the rabbit. Local mild ocular changes mainly consisting of redness and chemosis of the conjunctivae were transiently observed in the eye irritation study.

Immunotoxicity of dalbavancin was evaluated in rats treated at doses up to 40mg/kg during 28 days. Spleenic cell population (total absolute B-cell number, T-cell number, T helper cells, cytotoxic T-cells), humoral immunity (T-dependent antigen, sheep erythrocytes), cell-mediated immunity (T-cell proliferation, following T-cell receptor stimulation with anti-CD3 antibody) and innate immunity (NK cell assay) endpoints were addressed. Immunotoxicity NOEL in male and female rats were 10 and 40 mg/kg, respectively.
In male rats treated at 40 mg/kg, there was a statistically significant decrease in the humoral immune response when evaluated as specific activity or as total spleen activity (IgM plaque assay). All other immunological parameters (splenic cell population, cell-mediated immunity, and innate immunity) evaluated in the male rats were unaffected. According to the applicant, the biological significance of this was unclear as there was no consistent pattern of changes in cell population that correlated with the assay response, no evidence of a comparable effect in females, and no evidence of an increase in infections in rats or other consequences that were considered indicative of impaired humoral immune

response. Nevertheless, the applicant was requested to discuss the potential risks of this effect on patients taking also into consideration the clinical data available. The issue has been solved in the Responses Document.

Macrophage function has not been assessed in immunotoxicity studies. Histiocytosis, vacuoles or dark pigment were observed in macrophages in the repeated-dose toxicity studies and complete reversion was not achieved after recovery. In addition, in an in vitro study (GE028-03) mouse macrophages incubated in a solution of 14C-dalbavancin (20, 40, or 80 mg/L) had cell-associated concentrations of drug that exceeded that in the surrounding solution by factors between 5.9 and 25.5. Therefore, the applicant was requested to justify the lack of macrophage function assays. The issue has been solved in the Responses Document.

Regarding impurities, although Batch Analysis data for lots used in toxicity studies were included in Module 3.2.S.4.4., data for lot 029 differ from those provided in section 3.2.S.5-1 of the CTD (Please refers to relevant comments in the above Quality section). In addition to this, please, refer to relevant comments to Analytical Methods for calculation and expression of content of related substances in Quality section. Therefore, the applicant should provide a suitable tabulated overview of batches used in preclinical studies with their respective impurities profile taken into account such related Quality comments. An assessment of the impurities and specification levels that could be regarded toxicologically qualified in repeated-dose and genotoxicity studies was requested to be also included. The issue has been adequately clarified.

In a skin sensitization test in guinea pigs it was concluded that dalbavancin did not have contact sensitizing capacity.

No phototoxicity studies were performed. Although some elements of discussion were provided (UV spectroscopy characteristics including absorbance at 284 nm, considerations on structural similarity to known phototoxics), the lack of these studies is not considered justified taking into account the colouration of the compound, their long half-life and distribution to skin. Therefore, the need for a basic photosafety testing was requested to be reconsidered by the applicant. It has been adequately justified the lack of phototoxicity tests.

An Ecotoxicity/environmental risk assessment has not been submitted in the current MAA. According to the applicant, peptides are exempted because they are unlikely to result in significant risk to the environment (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, CHMP/SWP/4447/00). Nevertheless, it is also mentioned in this Guideline that substances with anti-microbial activity may affect microbial communities in environment and these effects should be evaluated. Therefore, the lack of ecotoxicity/environmental risk assessment studies was not considered justified and the applicant was requested to submit the ERA data. According to the Environmental Risk Assessment provided there is no concern on environmental risk from the use of dalbavancin.

III.3 Clinical aspects

Pharmacokinetics

The pharmacokinetics of dalbavancin were evaluated in 11 clinical studies:

Four (4) healthy volunteer studies, including two ascending dose studies with single-and multiple-dose regimens (VER001-1, VER001-2), as well as two excretion and distribution studies (VER001-10, VER-001-19). A total of 71 healthy volunteers were administered dalbavancin in these studies.

Four (4) studies in subjects with hepatic impairment (VER001-12), renal impairment, or subjects undergoing hemodialysis (VER001-3, VER001-11, VER-13). A total of 73 subjects were administered dalbavancin in these studies.

Three (3) patient studies (VER001-9, VER001-5, VER001-4), with data from a total of 532 patients that were combined and evaluated in a population pharmacokinetic analysis (VER001-PK01). Included in the analysis were 502 patients with SSSI.

Different variants of an LC/MS method were used to measure the concentration of the glycopeptide antibiotic dalbavancin and its main metabolite OH-dalbavancin in human plasma, urine and skin blister fluid, including dialysate. A microbiological assay was used to measure dalbavancin in faeces.

Both the validations and bioanalyses involved several different laboratories, and there were high variations between the recovery values obtained from different versions of the method. The reliability of the bioanalytical results of dalbavancin and OH-dalbavancin may be questioned due to inadequate validation of the analytical methods. The most prominent deficiency is the use of a ± 20% acceptance range in most of the validations supporting the bioanalyses. The possibility that dalbavancin may stick to plastic surfaces has not been discussed.

In their response the Applicant clarified that 20% acceptance in the validation of the analytical methods was employed because it was the state-of-the-art in the late 1990s. This acceptance criterion was modified globally in 2001 to a 15% for small chemical entities, but a 20% is used for peptides and proteins in binding assays. A wide acceptance range was also used because dalbavancin is a complex glycopeptide antibiotic with a high molecular weight amphipilic properties. Even with this wide acceptance criterion and some single measurements outside of this value, most values of accuracy and precision were within ±15%, moreover, the overall pre-study and in-study validation of the analytical methods can be considered acceptable because the primary pharmacokinetic variables (CL and Vss) are consistent across studies, and the inter-subject variability of dalbavancin clearance and the residual variance are low, which gives suggest that the residual variability of the study results is not inflated due to the analytical methods.

The Applicant has also submitted most of the validation protocols requested, but several are missing. Some other early validation reports lacked such protocols and were included as validation SOPs because this was the common practice in late 1990s. This is not of concern since both contains the same information in a different structure. A significant weakness of the validations is that long-term stability data from plasma and urine are compared only with the nominal values. Time zero data are missing. In addition, stability data at -20ºC for both skin blister fluid and faeces samples should have been elucidated, since the samples were stored at this temperature for extended periods of time. However, these deficiencies are seen as minor, since data stability is available for plasma and urine.

Although an inter-laboratory cross-validation between analytical methods employed in the different studies is lacking, the applicant has justified that the observed variability is low and the PK parameters are consistent across-studies.

The applicant claims an approximate 10% loss after a single transfer for urinary samples (not in plasma) due probably to its adsorption to polypropylene tubes, which explain the incomplete accountability of the administered dose (only 70% could be accounted for). However, the report of this recent investigation has not been provided and it should be submitted (see RSI).

Maximum concentration of dalbavancin in plasma (C_{max}) was achieved immediately following the end of infusion. The mean C_{max} following 1000 mg IV dalbavancin in healthy subjects was 250-340 mg/l, and the volume of distribution (Vss) was 11.2-18.5 l. This is approximately 20% of body weight, consistent with the theory that the drug is distributed in the extracellular fluid. Dalbavancin is highly bound to plasma proteins (93.1%) and does not seem to have any relevant distribution into the red blood cells. The relative exposure of dalbavancin into skin (AUCskin/AUCplasma) was approximately 36%, and the relative exposure of dalbavancin in skin blister fluid was approximately 60%.

Dalbavancin was not metabolized by human hepatocytes, liver microsomes, or kidney microsomes. Dalbavancin did not inhibit the activity of CYP1A2, 2A6, 2B6, 2C19, 2C9, 2D6, 2E1, or 3A4 in an in vitro assay using human microsomal enzymes. Two dalbavancin metabolites, OH-dalbavancin and mannosyl aglycone (MAG), have been found in human urine and in human plasma samples. MAG is

one of the impurities in the drug substance, but may also be produced in vivo by biotransformation or degradation. The enzymes responsible for the conversion of dalbavancin into OH-dalbavancin and mannosyl aglycone have not been characterized. The presence of OH-dalbavancin and mannosyl aglycone is regarded clinically insignificant because of the low levels observed in plasma and because the metabolites are less active than dalbavancin. Even though the concentrations of the metabolites are low in plasma, OH-dalbavancin in urine represent about 10% of the total dose or about 40% of the dose excreted in urine, which is not insignificant. As hydroxylation reactions often are exerted by CYP enzymes, the applicant should justify that the submitted studies exploring involvement of CYP enzymes are adequate.

In their response to the Day 120 List of Questions the Applicant has justified that the knowledge of the enzymes_responsible for formation of hydroxy-dalbavancin and mannosyl aglycone would be of limited clinical significance because hydroxylation is only a minor clearance mechanism for intravenous administered dalbavancin and the relative contribution of this metabolic pathway is only 15% approximately, as confirmed by the lack of effect of treatment with CYP inhibitors on the clearance of dalbavancin in the population PK analysis. There is no reason to assume that the in vitro studies are not methodologically adequate.

Dalvabancin is eliminated as intact drug by renal excretion (33%) and in feces (20%). In healthy subjects, CL was found to be 0.038-0.051 l/h. The amount of drug excreted unchanged in the urine was 19-33% of the administered dose, and the amount of the metabolite OH-dalbavancin excreted in the urine was 8-12% of the total dose. The excretion of dalbavancin into feces was about 20% of the administered dose. Thus, only approximately 70% of the administered dose could be accounted for in urine and feces. The applicant suggests that the remaining 30% of the administered dose is also likely to be excreted in urine and feces, but may be eliminated at slower rates in the later points in the profile with concentrations in urine and feces that fall below the quantifiable limits of the assays. However, the lack of a mass-balance study and characterisation of dalbavancin-related material in plasma is of concern. The Applicant should provide reassurance that there are no unidentified metabolites at significant levels in humans that are not present in the species used in preclinical toxicology studies. In their response, the applicant argued that a highly sensitive LC/MS/MS technique with multiple reaction monitoring would have been able to detect dalbavancin metabolites if present in human plasma and urine if they had been present. Therefore, there are no unidentified metabolites at significant levels in humans that are not present in the species used in toxicology studies and the need for a mass-balance study is not considered necessary. This is accepted.

The disposition of dalbavancin is described to be tri-phasic, with a short initial distribution phase with half-life (T½) of approximately 2.5 h, an elimination phase that accounts for the majority of drug elimination with T½ of approximately 5 days, and a terminal elimination phase with a T½ of 16 days. However, it is not clear how the applicant deduced the three phases of dalbavancin disposition. Mean T½ in healthy subjects receiving a regimen of 1000 mg (day 1) plus 500 mg (day 8) dalbavancin was 13.4 days. The mechanism(s) behind the long T½ is not known. However, this long half life is of concern regarding potential adverse events. The applicant has submitted the concentration – time plot showing the three phases of disposition. In addition, reanalysed data from study VER001-19 shows that the tri-compartmental model is the one that provides the best goodness of fit. This analysis confirms the estimates of the half-lives of three phases.

The Applicant should address the extremely low renal clearance in relation to the mechanism of renal excretion since this information is necessary to interpret the drug pharmacokinetics. The Applicant has identified net renal tubular re-absorption of dalbavacin and its low extraction as possible explanations for the prolonged half-life of dalbavancin.

Pharmacokinetics of the metabolites has not been characterized because they are not measurable in plasma. Dose proportionality has been investigated in a descriptive way. Although a formal statistical analysis is missed to obtain confirmative evidence of such dose proportionality as proof of linear pharmacokinetics, it is not considered a concern based on the descriptive evidence and the low variability of the drug. Time independency has not been assessed properly at therapeutic doses, but it

is not considered essential because the drug is not administered chronically but simply as two single dose administrations of 1000 mg on day 1 and 500 mg on day 8. Inter-individual variability of the drug has shown to be low (<30%) and, although the intra-individual variability has not been discussed, it can be assumed to be low as well.

The pharmacokinetics in the patient population is similar to the pharmacokinetics in healthy volunteers, i.e. the population pharmacokinetic model, using data from the target population, describes a situation with T½ of 8.5 days and CL of 0.057 l/h.

Dalbavancin exposure after administration to subjects with normal renal function and subjects with mild renal impairment (CrCL < 80 ml/min) was similar, while a small increase in concentrations was observed in subjects with moderate renal impairment (CrCL < 50 ml/min) beyond day 14. In severe renal insufficiency (CrCL < 30 ml/min) the AUC increases approximately two-fold. The effect of renal function appears to be less pronounced on the basis of the population model, which may be due to that very few patients with low renal function (CrCL < 50 ml/min) were included, a linear relationship was assumed for the CL-CrCL relationship (a non-linear relationship or truncation of high CrCL values appears to have been more appropriate) and/or the effect of renal function was masked due to the additional effect of body surface area (BSA) on CL. Thus, the effect of renal function should be judged from the renal impairment studies. In patients with end stage renal disease (ESRD) undergoing regularly scheduled dialysis, dalbavancin exposure was similar to subjects with normal renal function, in spite of no measurable dalbavancin or dalbavancin metabolite in the dialysate. There seemed to be higher concentrations of OH-dalbavancin in subjects with ESRD and severe renal impairment than in subjects with normal renal function. The mechanism for the possible compensation in clearance of dalbavancin in patients with ESRD undergoing regularly scheduled dialysis is not known. In their response, the Applicant clarified that in patients with ESRD undergoing regularly scheduled dialysis, dalbavancin was detected below the level of quantification (1 mg/ml). This small amount in a large volume of dialysate (2432 litres approximately) may account for a significant amount of the administered dose (16-40%). This may explain why dialysis may compensate the renal insufficiency, although it has not been verified.

For patients with a CrCL < 30 ml/min without receiving regularly scheduled haemodialysis, the proposed posology is 750 mg dalbavancin (Day 1) followed by 375 mg dalbavancin (Day 8) based on simulations. This should be further discussed. For patients with a CrCL < 30 ml/min without receiving regularly scheduled haemodialysis, the proposed posology is 750 mg dalbavancin (Day 1) followed by 375 mg dalbavancin (Day 8) based on simulations. This should be further discussed. Taking into account that the proposed posology for patients with severe renal impairment is based on simulations it is important to remember that there is limited clinical experience in these patients and no experience with the proposed posology. However, the Applicant has reasonably shown that systemic exposure in patients with severe renal impairment (CrCL < 30 ml/min) at the proposed posology is similar to that attained in patients with normal renal function. Thus it is proposed to keep current dosage recommendation in the SPC provided that adequate information is given about the limitations, i.e. recommendation based on simulations, limited experience in patients with CrCL < 50 ml/min etc. The CHMP however considers that this aspect would deserve further evaluation and the Applicant should present a proposal on how this aspect is intended to be further studied.

In case of hepatic impairment, clearance in dalbavancin pharmacokinetic parameters appeared to be partially influenced by the drug's distribution volume. Volumes of distribution increased in the same proportional manner as CL; therefore, the drug terminal elimination half-life was virtually unchanged across the groups. Consequently, no dose adjustment for patients with moderate or severe hepatic impairment is recommended in the SPC. However, although the mean value of AUC in severe liver impaired patients is within the range of AUCs of healthy volunteers there is one case out of five with a systemic exposure 2-fold lower than the mean AUC observed in healthy volunteers. As such a change might be clinically relevant the Applicant should address the reasoning for an increased clearance in severe and moderate hepatic insufficiency and the reason for such an outlier value. The Applicant has explored again the existing data, but it is not able to find a cause to explain the decreased extent of exposure (AUC) in subjects with severe hepatic impairment. The Applicant is only able to justify that

the cause is not related to a change in the extent of protein binding. It has been clarified that there is an overlapping between the concentrations and AUC observed in severely impaired patients and normal subjects. As unbound plasma concentrations over the entire treatment period is well above the range of MICs there is no evidence that this decrease in exposure has clinical relevance. Therefore, the recommended caution is considered an acceptable solution and no dosage adjustment seems to be necessary. This is accepted.

The population PK analysis cannot be considered conclusive with respect to the assessment of covariates for several reasons. The identification of covariates to be tested within NONMEM was based on exploration (graphical and GAM analysis) of empirical Bayes estimates of the parameters without an assessment of the shrinkage towards the population mean. Thus, in the case of shrinkage (sparse sampling was employed) important covariate parameter-relationships may have been ignored. Age, gender and race seem to have been investigated in the GAM analysis but not within NOMMEN. With respect to age there appears to be sufficient clinical data to conclude that dose adjustments are not necessary in the elderly. Weight or body surface area was considered as relevant covariate in the population PK analysis but it was not considered as clinically significant. In spite of this, the impact of weight needs to be further addressed as data on AUC and/or Cave/Cmin in this patient population have not been discussed. The Applicant has investigated the population included in the Pop-PK study to address the relevance of body weight in the concentration – time profile. In particular in Cmax after the first dose and Cmin just before the second dose. Patients have been classified according to their BMI and the differences between groups are of a minor magnitude and there is a considerable overlap. Therefore, these differences seem to lack of any clinical relevance. A dosage adjustment based on body weight or body surface area is not necessary. No information about pharmacokinetics in children is available. Therefore, no recommendations for this age group are possible.

Specific clinical interaction studies were not performed. Population pharmacokinetics was used to screen for possible interacting concomitant drugs. The only statistically significant variable found was the presence of cytochrome P450 inducers, increasing the CL of dalbavancin by less than 10%. However, the run records reveal deficiencies in terms of local minima, thus indicating a problem in the data or the model. Further, it is not acceptable to group all CYP450 substrates, inhibitors and inducers, respectively, and use those as covariates. Taken into account the lack of knowledge of the metabolic fate of the drug, including the 30% of drug not accounted for in elimination, the unexplained long terminal half-life, and the weaknesses of the analytical methods, the applicant should discuss the reliability in not exerting specific clinical interaction studies. The Applicant has clarified that that specific clinical drug-drug interaction studies are not necessary because only a minor part of the drug is metabolised (15% approx.). The long terminal half-life may be caused by net renal re-absorption and low hepatic extraction. It is also unlikely a DDI caused by another drug with high protein-binding.

Pharmacodynamics

Dalbavancin, a so-called second-generation glycopeptide, is structurally related to teicoplanin. Although all glycopeptides share a same basic mechanism of action, i.e., the formation of a complex with the C-terminal d-alanyl-d-alanine of growing peptidoglycan chains, thereby inhibiting bacterial cell wall biosynthesis, detailed structure-activity relationship studies (Van Bambeke, 2004) have demonstrated that some subclasses are more effective than others. In this regard, and compared with typical glycopeptides, dalbavancin is said to be active against VanB and VanC enterococci and to posses enhanced activity against staphylococci, particularly coagulase-negative staphylococci (CoNS).

Mechanism of action/mechanism of resistance

While it is agreed that the inhibition of peptidoglycan synthesis is the main mechanism of action, no further explanation is provided to support the differences in antibacterial activity between dalbavancin and teicoplanin, e.g. whereas reduced susceptibility or resistance to teicoplanin is regularly observed among coagulase-negative staphylococci (CoNS), dalbavancin shows good activity against these strains. In addition, to account for the differences between teicoplanin and dalbavancin, as compared

to vancomycin, against enterococci harbouring the modified van D-alanyl-D-serine (D-ala-D-ser) peptide terminus, a higher affinity of the two former has been pointed out.

The Applicant should further discuss this issue, i.e. the details of the inhibition of peptidoglycan synthesis responsible for the differences in antibacterial activity between dalbavancin and classical glycopeptides. In their response to the Day 120 List of Questions the Applicant clarified that dalbavancin has the potential for direct interaction with transglycosylase by direct binding, unlike the classical glycopeptides. This is assumed to be the mechanism behind the differences in potency between dalbavancin and classical glycopepetides.

No emergence of resistance to dalbavancin was detected in animal infection experiments, or *in vitro* studies designed to detect development of resistance. Thus, the potential for emergence of resistance to dalbavancin in *S. aureus* appears to be low. However, data from similar studies on streptococci should be discussed. In their response the Applicant states that the presence of the VanA gene cluster in another bacterium capable to provide a naive bacterium with the resistance gene cluster necessary to induce glycopeptides resistance has not been shown. This may well be true at present. Given the properties of dalbavancin one may, however, expect that both staphylococci and streptococci located in other areas in the human body may be exposed over a longer period of time to low concentrations of dalbavancin and that might induce low grade resistance. This problem could be answered by examining the status of follow up isolates from patients who have been treated with the drug but where there was partial bacteriological cure or failure. Such data should be presented.

Dalbavancin antibacterial activity should not be affected by several mechanisms of resistance such as methicillin-resistance in Staphylococci and penicillin-and/or erythromycin-resistance in Streptococci. Similarly, resistance to linezolid and daptomycin is not expected to affect the antibacterial activity of dalbavancin as the target of these antimicrobial agents also differed from the target of dalbavancin. However, since dalbavancin shares the same target as classical glycopeptides (inhibition of peptidoglycan synthesis) there is a basis for cross-resistance between them.
Clinically relevant glycopeptide resistance occurs in Enterococcus spp. and very rarely in Staphylococcus spp. Glycopeptides do not exhibit complete cross-resistance, e.g. some vancomcyin-resistant enterococci (VRE) phenotypes are susceptible to teicoplanin and most teicoplanin-intermediate CoNS susceptible to vancomycin. Trully teicoplanin-resistant CoNS have usually decreased susceptibility to vancomycin. According to the Applicant, dalbavancin is active against strains that are susceptible to either teicoplanin or vancomycin, i.e. it is active against teicoplanin-susceptible VRE (VanB and VanC phenotypes) and also against teicoplanin-resistant CoNS. Additionally, dalbavancin is active against vancomycin-intermediate S. aureus (VISA) strains (although higher MICs are oberved).

In spite of all this, there is a concern about the potential to select in vivo non-susceptible strains in case of previous treatment with vancomycin (mainly if prolonged) as well as when treating vancomycin-intermediate staphylococci given the higher MICs in these cases. In addition, emergence of resistance to teicoplanin has been described in VRE (VanB phenotype) during treatment with this antimicrobial agent and similarly the potential development of resistance to dalbavancin could not be ignored. Therefore, the Applicant should address the concerns on the development of in vivo resistance to dalbavancin in patients infected with glycopeptide-intermediate staphylococci and with enterococci (VanB phenotype). In addition, cross-resistance is also a concern in the case of coagulase-negative teicoplanin-resistant staphylococci. If warranted appropriate information should be included in section 5.1. In the response the Applicant concludes that based on the in vitro activity of dalbavancin as well as in the absence of emergence of resistance in clinical trials, there is little likelihood that resistance to dalbavancin will develop in vivo. However, data available are too limited to draw this conclusion for the time being. Especially, treatment of the strains of concern will be critical for the assessment of the potential of dalbavancin to induce resistance. Further data are needed to better assess the potential of resistance induction due to dalbavancin in a clinical setting.

The Risk Management System states that dalbavancin will be included in two surveillance studies. The adequacy of both surveillance programs for the European Union should be addressed. The

Applicant is requested to address the feasibility of an extended surveillance program in the European Union. In their response the Applicant states that there is an ongoing programm in the European Union that uses disk-diffusion methodology (E-test and disk diffusion). However, according to the information provided disk diffusion is not suitable for dalbavancin. A question has been raised in this regard in the section on RMP. Furthermore, the three protocols of the surveillance studies should be submitted.

Spectrum of in vitro activity and relevant pathogens for the claimed indication

Dalbavancin has a similar spectrum of in vitro activity to the classical glycopeptides, but overall it seems more potent than vancomycin or teicoplanin.

Most data presented on the in vitro activity of dalbavancin has been extracted from a prospective worldwide survey conducted in 2003 (unless otherwise specified) in which approximately 9,007 Gram-positive (including MSSA, MRSA and CoNS) patient isolates from Europe (45%), Latin America (15%) and North America (41%) and 1,497 strains of beta-haemolytic and non-beta-haemolytic, penicillin-susceptible and non-susceptible streptococci have been tested.

In this survey, dalbavancin showed a MIC90 of 0.06 µg/mL against both methicillin-susceptible (n=2834) and methicillin-resistant (n=1119) strains of *S. aureus*; the MIC ranged from ≤0.008-0.25 µg/mL and 0.015-0.25 µg/mL, respectively.

Against coagulase-negative staphylococci, MIC90 and MIC range were 0.06 µg/mL and ≤0.008-1 µg/mL for methicillin-susceptible strains (n=353) and 0.12 µg/mL and ≤0.008-1 µg/mL for methicillin-resistant strains (n=1129). In a European retrospective survey, against 20 CoNS isolates with reduced susceptibility to teicoplanin (MIC≥8 mg/L), dalbavancin MICs ranged from 0.03 to 0.12 mg/L (MIC90 0.12 mg/L). Table below shows this data as well as MIC90 and MIC range for certain comparators.

Activity of dalbavancin and other agents against clinical isolated staphylococci from 2003 worldwide survey

Compound	*Staphylococcus aureus*				*CoN staphylococci*			
	MSSA		**MRSA**		**MSCoN**		**MRCoN**	
	MIC 90	**MIC Range**	**MIC 90**	**MIC Range**	**MIC 90**	**MIC Range**	**MIC 90**	**MIC Range**
Dalbavancin	0.06	≤0.008 – 0.25	0.06	0.015– 0.25	0.06	≤0.008- 1	0.12	≤0.008- 1
Teicoplanin	≤2	≤2 - 4	4	≤2 – 8	4	≤2 - 16	4	≤2 - 8
Vancomycin	1	0.5 - 2	2	0.25 – 2	2	0.5 – 2	2	≤0.12 - 4
Linezolid	2	0.12 - 8	2	0.25 – 2	1	0.25 – 2	1	0.25 - 2
Daptomycin	0.25	0.12 - 1	0.5	0.12 – 1	0.5	0.12 – 1	0.5	0.12 - 2
Clindamicyn	0.12	≤0.06 - >8	>8	≤0.06 - 8	0.12	≤0.06 - >8	>8	≤0.06 - >8

S. epidermidis was the most frequently represented species of CoNS, with a total of 953 isolates in 3 studies (one of them the above mentioned survey). However, more than 1000 CoNS isolates from two prospective surveys were not identified to species level. Most dalbavancin MIC90s by species and study ranged from 0.03 to 0.12 mg/L. Exceptions included *S. haemolyticus*, for which MIC90s were 0.25 and 0.5 mg/L in two studies, and *S. saprophyticus*, for which the MIC90 was 0.25 mg/L in one of the 3 studies. Dalbavancin MIC50s for *S. haemolyticus* were 0.12 mg/L in all 3 studies, whereas for other species MIC50s were usually ≤ 0.03 mg/L. Isolates of this species included those with the highest teicoplanin MICs.

In a study performed with strains from culture collections and the Network on Antimicrobial Resistance in Staphylococcus (NARSA), dalbavancin MIC range and MIC90 against heterogeneous vancomycin-intermediate *S. aureus* (hVISA) (n=21), were 0.06-1 mg/L and 1 mg/L, respectively (see table below). The low number of the remaining strains [vancomycin-intermediate S. aureus (VISA), heterogeneous vancomycin-intermediate coagulase-negative staphylococci (hVI-CoNS) and vancomycin-intermediate CNS (VICoNS)] precluded the calculus of a MIC90 value, but it should be noted that dalbavancin MIC ranged from 0.5-1 mg/L for VISA and hVICoNS and from 0.25-2 mg/L

against VICoNS, raising concern about the potential for developing resistance of these strains with higher MICs.

Agent	MIC range (mg/L)					
	hVISA n=21	**VISA n=4**	**VRSA n=2**	**LIN NS n=5**	**hVI-CoNS n=6**	**VICoNS n=5**
Dalbavancin	0.06 –1 MIC90: 1	0.5 – 1	2*- 16	0.03 - 0.06	0.5 - 1	0.25- 2
Vancomycin	1-4	8	> 32	0.5 - 2	4	8
Teicoplanin	1 - 16	4 – 32	8 - 32	0.5 – 2	8 - >32	16 - >32
Linezolid	1 - 2	1 – 2	2	8 - >16	0.25 - >8	0.25 - >8
Quinupristin/dalfopristin	0.25 - 1	0.25 – 0.5	0.5 - 1	0.25 – 0.5	0.25 – 0.5	0.25 – 0.5
Trimetropim/sulfametoxazole	≤0.25 - >4	0.25 – 4	4 - >4	≤0.25 - >4	0.5 - >4	≤0.25 - >4

Saravolatz (2005) tested dalbavancin against 23 CA-MRSA isolates. The MIC90 of dalbavancin was 0.03 mg/L.

Dalbavancin MIC90 against *S. pyogenes* (n=173) was 0.015 µg/mL (range ≤0.008-0.12 µg/mL) and against other beta-haemolytic streptococci (groups B, C, F, G, n=216) was 0.03 µg/mL (range ≤0.008-0.12 µg/mL). For the viridans group streptococci (136 isolates) MIC90 was 0.03 µg/mL (range ≤0.008-0.12 µg/mL), regardless of penicillin resistance phenotype. The activity of dalbavancin was comparable to that of penicillin against penicillin susceptible strains.

The frequency distribution of MICs for *Streptococcus* spp. does not seem to be as homogeneous as for *S. aureus* isolates, i.e. there seem to be two groups of *Streptococci* in the population; a sensitive and a less sensitive group. The species which dominate the less sensitive part of the population as well as those with the highest MIC values should be specified. In addition, the applicant is requested to address the possibility of an underlying resistance mechanism for *Streptococci.* In response to this concern the in vitro sensitivity data for both staphylococci and various streptococci has been reviewed. The data on both *S. aureus* (ORSA) and beta-haemolytic streptococci (BHS) show that the sensitivity of these isolates are clustered so that variation most likely is a result of methodology and not so much as a consequence of strain qualitative difference in dalbavancin sensitivity. However, one might wonder whether the less sensitive part consists of isolates that have been exposed to glycopeptides previously. The applicant has not discussed this issue. This should be addressed.

In vitro, dalbavancin is active against vancomycin-susceptible enterococci [MIC90 against *E. faecalis* (1,324 isolates) and *E. faecium* (n=189) strains was below 0.25 µg/mL; MIC range against vancomycin-susceptible *E. faecalis* was ≤0.008-0.12 µg/mL whereas against vancomycin-susceptible *E. faecium* was ≤0.008-2 µg/mL]. Against vancomycin-resistant strains dalbavancin had higher MIC90 values, i.e. ≥16 µg/mL. The MIC ranges for vancomycin-resistant *Enterococcus faecalis* (108 isolates) and *Enterococcus faecium* (364 isolates) were 0.03 - >16 µg/mL and ≤0.008 - >16 µg/mL, respectively. In the worldwide survey no genotypic information was available and strains were classified, i.e. vanA, vanB etc. based on their phenotypic features.

Table below shows this data (2003 worldwide survey).

	S. pyogenes		***Streptococcus* spp. *Groups B,C,F,G***		**Viridans Group *Streptococci***			
					Pen-S		**Pen-NS**	
	MIC_{90}	**MIC Range**	**MIC 90**	**MIC Range**	**MIC 90**	**MIC Range**	**MIC 90**	**MIC Range**
Dalbavancin	0.015	≤0.008-0.12	0.03	≤0.008-0.12	0.03	≤0.008-0.12	0.03	≤0.008-0.06
Vancomycin	0.5	≤0.25 – 1	1	≤0.12 – 1	1	≤0.25 – 1	0.5	0.25 – 2
Penicillin	0.06	≤0.015-0.12	0.06	≤0.015- 1	-	-	-	-
Linezolid	1	≤0.06 -2	1	≤0.06 -2	1	≤0.12 -1	1	0.25 – 1
Daptomycin	0.12	0.03-0.12	0.25	0.03 – 0.5	1	≤0.015- 2	1	0.12 – 2
Clindamicyn	≤0.06	≤0.06- >8	≤0.06	≤0.06- >8	0.25	≤0.06- >8	8	≤0.06 - >8
	Enterococcus faecalis				***Enterococcus faecium***			
	Van-S		**Van -R**		**Van -S**		**Van -R**	
	MIC_{90}	**MIC Range**	**MIC 90**	**MIC Range**	**MIC 90**	**MIC Range**	**MIC 90**	**MIC Range**
Dalbavancin	0.06	≤0.008-0.12	>16	0.03- >16	0.12	≤0.008- 2	16	≤0.008- >16
Teicoplanin	-	----	>16	≤ 2 – 16	-	----	>16	≤2 - >16
Vancomycin	2	0.25 – 4	>16	8 - >16	2	0.25 – 4	>16	2 - >16
Linezolid	2	0.25 – 4	2	1 - >8	2	0.5 - >8	2	1 – 8
Daptomycin	1	0.12 – 2	2	0.25 - 2	-	2 – 4	4	0.25 -8
Penicillin	8	≤0.015- >32	16	1 - >32	>32	0.12 - >32	>32	1 - >32

In a different study where genotypic information was available, VanA phenotypes generally had higher dalbavancin MIC results (MIC50/90, ≥8/≥8 mg/L), although some strains that had vanA genes proven by PCR tests, exhibited low, reproducible dalbavancin values (0.06 to 0.5 mg/L). VanB phenotypic strains were more dalbavancin-susceptible, but elevated dalbavancin MIC results (≥1 mg/L) were described for some strains (6 isolates), although not all of them had detectable vanB (3 isolates). Lastly, vanC expressing species (37 *E. casseliflavus* and *E. gallinarum*) were inhibited by dalbavancin at ≤0.25 mg/L, except for five isolates that acquired a vanA gene (dalbavancin MIC, ≤2 mg/L).

Dalbavancin activity against some Gram-positive anaerobes such as *Actinomyces* spp., *Clostridium* spp. (with the exception of *C. clostridioforme*), *Eubactaerium*, *Peptostreptococcus* spp. and *Propionibacterium* spp. has been shown in agar dilution method. β-lactam comparators had potent activity against *Propionibacterium* spp and *Peptostreptococcus* spp. Dalbavancin almost lacks activity (MICs ≥32 mg/ml) against *Lactobacillus acidophilus* and *Lactobacillus casei* but was active against *Lactobacillus fermentans* (MICs ≤0.25 mg/ml). However, what seems really relevant is whether dalbavancin is or not active against vancomycin-resistant lactobacilli and can constitute an alternative for these difficult-to-treat microorganisms.

Dalbavancin showed activity against *Bacillus* spp. and *Listeria* spp. with MIC90 values of 0.5 and 0.06 mg/L, respectively. Against different species of *Corynebacterium* MIC90 (agar dilution) was 0.5 µg/mL and similar activities were attained by linezolid and vancomycin. Daptomycin showed low MICs against *Corynebacterium jeikeium* (MIC90 = 0.06µg/mL) and Corynebacterium amycolatum (MIC90 = 0.25 µg/mL) but higher against *Corynebacterium* spp. (MIC90 = 8 µg/mL).

Bactericidal activity is usually defined as a MBC:MIC ratio of ≤4. While it is agreed that overall dalbavancin demonstrated lower MICs and MBCs than those of vancomycin and teicoplanin and other comparators against a number of species of interest, based on the MBC:MIC ratios attained in this study, dalbavancin cannot be assumed as uniformly bactericidal against all of them. Furthermore, for some strains it should be noted that quite higher MBC values were attained as compared with the corresponding MICs, e.g. for one of the strains of viridans streptococci tested (*S. intermedius* 1110271) the MIC value was 0.03 mg/L whereas MBC value was 1 mg/L (dalbavancin MBC:MIC ratio of aprox. 33 as compared with 4 for penicillin). The same applies to *S. pyogenes*1110155 (MBC:MIC ratio of aprox. 31 as compared with 4 for penicillin), MSSA1109397 (MBC:MIC ratio of 16 as compared with 8 for oxacillin), MRSA1109400 (MBC:MIC ratio of aprox. 8 as compared with 1

for both vancomycin and teicoplanin) and to *S. haemolyticus*1109812 (MBC:MIC ratio of aprox. 4 as compared with 1 for teicoplanin). As expected, the highest MBC:MIC ratios were attained against enterococci. For one single strain of VISA tested, dalbavancin MBC:MIC ratio was 2. The Applicant is requested to discuss the MBC:MIC ratios attained in this study (Report 1459B-102) in the light of the previous comments, including the differences observed within different strains of the same species. Based on the Applicant's response the CHMP still considered that dalbavancin cannot be assumed as uniformly bactericidal (MIC:MBC ratios ≤ 4) against all of these strains. In addition, no studies were done to measure the effect of P-80 on the MBC values. However, this issue is not deemed critical provided that appropriate changes are introduced in the SPC.

Time kill kinetic studies have shown that the antibacterial activity of dalbavancin is time-dependent and time-kill curves similar to those of usual glycopeptides are attained when the wetting agent polysorbate-80 (P-80) is added. The addition of 0.002% of P-80 has been approved by CLSI for testing dalbavancin MIC in broth microdilution (except when using dry-form microtitre panels). In the time-kill kinetics presented 0.02% of P-80 was added, but the consequences of this are barely mentioned. The Applicant should further discuss the consequences for the interpretation of the time kill kinetics of adding 0,02% polysorbate-80 instead of 0.002%. The Applicant has adequately addressed this issue in their response.

Overall, in time kill kinetics a similar bactericidal activity (decrease of at least 3 log10 in CFU) is attained with three of the doses tested, i.e. 1, 4 and 16 mg/L whereas regrowth is seen almost uniformly with the lowest dose of 0.25 mg/L. According to the Applicant, these concentrations were chosen to span potential maximum and minimum (Cmax and Cmin) plasma levels of unbound dalbavancin (approximately 18 and > 1 mg/L, respectively) in humans treated with the proposed dosage regimens. Cidal activity was shown against the three strains of methicillin-susceptible *S. aureus* as well as gainst methicillin-resistant *S. aureus*. One single vancomycin-intermediate *S. aureus* (VISA) strain was tested. Dalbavancin also showed cidal activity against this strain. Time-kill kinetics were also performed for vancomycin and teicoplanin, showing a similar pattern to that of dalbavancin, although for some strains, e.g. the VISA strain, the degree of killing was less (about 1 log10 CFU/mL less killing than for dalbavancin). Unfortunately, it appears that in these experiments oxacillin (or similar) and penicillin were not included as comparators. Consequently, regarding methicillin-susceptible *S. aureus* and streptococci (other than *S. pneumoniae*) the Applicant should discuss the in vitro bactericidal activity of dalbavancin in comparison with that of semi-synthetic penicilins (MSSA) and penicillin (streptococci). These data have not been provided in the response to the Day 120 List of Questions as they are not available. Based on the Applicant's response the single conclusion that can be drawn is that *in vitro* dalbavancin shows good activity against methicillin-susceptible *S. aureus* as compared with oxacillin and against *S. pyogenes* as compared with penicillin. However, the pharmacodynamics properties of dalbavancin compared with both beta-lactams are not known. In spite of this it is considered that this issue is solved given that in the current SPC *S. pyogenes* is listed but no asterisk denoting that efficacy has been shown is added.

One single strain of *S. pyogenes* has been tested in time kill kinetics. Although it is concluded that bactericidal activity with a 5 log10 CFU/mL kill at concentrations ≥ 1 mg/L was shown for dalbavancin, whereas vancomycin and teicoplanin were less bactericidal (about 2 log10 CFU/mL reduction in titer) it should be noted that growth of the control strain appears somehow impaired (autolysing).

In time kill studies bactericidal activity against microorganisms in the exponential phase of growth was shown except in the case of *S. pyogenes*. The Applicant should clarify whether there is activity against microorganisms in stationary phase of growth and for *S. pyogenes* in the exponential phase. Regarding the activity against microorganisms in the stationary phase of growth the Applicant's response is not endorsed nor the explanation given for *S. pyogenes* (see also Assessment of the Applicant's response to other concern 155). In spite of this the issue is considered solved as the overall impact in the assessment is deemed to be minor.

For antimicrobials it is in general assumed that highly (>80%) serum protein binding adversely affects their antimicrobial activity. Several studies have been conducted to address the issue for dalbavancin given its high percentage of protein binding (about 93%). Overall, in these experiments the addition of

50% human serum resulted in a variable MIC increase of the strains tested suggesting that the presence of human serum impairs the in vitro activity of dalbavancin. As a consequence, the effect of protein binding on the *in vitro* activity of dalbavancin should be discussed considering the statement "the extent of the serum effect was somewhat variable by strain, methodology, and laboratory" from the Clinical Overview, and recommendations should be clearly given to assure intermediate precision (intra-lab) and reproducibility (inter-lab). In their response, the applicant claims that the observed MICs when exposed to serum were still below sustainable serum levels of dalbavancin for all of the strains. The applicant concludes that these MBC values are well below the minimum plasma levels of dalbavancin observed over the entire treatment period in humans. The applicant refers several studies which show that the MIC and the MBC varies but no exact protocol is suggested to harmonize these findings. Albeit seldom needed in patient care, the applicant should propose a protocol to which potential users should adhere when MIC and/or MBC are to be recorded.

Most antibiotics that act by inhibiting cell wall synthesis such as glycopeptides routinely produce a postantibiotic effect (PAE) with staphylococci, but less so with streptococci. The in vitro PAE of dalbavancin was determined against 4 strains of *S. aureus*, which included a MSSA strain, a MRSA strain and 2 VISA isolates. PAE values for dalbavancin were relatively short (ranged from 0.8 hours against a VISA strain to 2.9 hours against MRSA ATCC33591) and similar to those of teicoplanin and vancomycin. No PAE determination was performed for streptococci. Consequently, data on the PAE on streptococci should be discussed. The applicant has argued that a post-antibiotic effect is not a very major factor in the efficacy of dalbavancin. The arguments seem appropriate as far as the clinical effects are concerned. However, this aspect should be observed as a part of post-marketing program in order to investigate the possibility of resistance development.

Broth microdilution should be used for dalbavancin MIC testing. Dry-form panels were used for broth microdilution MIC determinations in all of the clinical studies and most of the non-clinical studies of dalbavancin. Dry-form trays did not require addition of a wetting agent such as polysorbate-80 (P-80). Whereas omission of P-80 may raise the apparent MIC of dalbavancin by about 2 dilutions when using freshly prepared or frozen microtitre trays, results with the dry-form panels are the same with or without P-80. Current CLSI recommendations for testing dalbavancin in vitro are as follows (CLSI document M100-S17): the solvent and diluent for preparation of stock solutions of dalbavancin is dimethyl sulfoxide (DMSO). Starting stock solutions of dalbavancin should be prepared at concentrations no higher than 1600 µg/mL. Intermediate 100x concentrations should then be diluted in DMSO. Final 1:100 dilutions should then be made directly into Cation-Adjusted Mueller-Hinton Broth supplemented with 0.002% (v/v) polysorbate-80 so that the final concentration of DMSO in the wells is not greater than 1%.

The CLSI approved (CLSI 2005) Quality Control strains and their respective ranges for the broth microdilution MIC method are as follows:

- *E. faecalis* ATCC29212; MIC range (mg/L):0.03-0.12
- *S. aureus* ATCC29213; MIC range (mg/L): 0.03-0.12
- *S. pneumoniae* ATCC49619: MIC range (mg/L):0.008-0.03

Agar dilution methodology has been used to determine dalbavancin MICs for anaerobes and, in limited studies, for some bacteria that grow aerobically. Comparatively, higher MICs are attained with agar dilution versus broth microdilution. Standardisation of the agar dilution method and determination of QC limits with this method have not been completed.

Dalbavancin activity against *S. aureus* and *Streptococcus* spp. could be predicted by vancomycin for vancomycin-susceptible organisms. However, vancomycin should not be used as a surrogate for dalbavancin for susceptibility testing in case of nonsusceptible vancomycin isolates. In this instance, dalbavancin MIC testing should be performed.

Studies have been conducted by AB Biodisk with the aim of developing an E-test for dalbavancin susceptibility testing. It is anticipated that this test will be available commercially in June, 2007.

The Applicant is requested to provide a manual with current recommendations for testing dalbavancin in laboratories of Microbiology. In particular, the following issues related to the primary sensitivity testing of dalbavancin need further clarification:

a) The impact of using a wetting agent (P-80) or DMSO on the observed in vitro activity of the compound should be elaborated in more detail. A possible interaction between these compounds and dalbavancin (or other antibacterial agents) should be ruled out. It should also be elucidated how much the observed *in vitro* MIC and /or MBC values would increase when omitting these agents.

b) The applicant should present data on the use of disc diffusion method for primary sensitivity testing and state if there are any particular measures to be taken into consideration when using such methodology. If this method is not applicable for dalbavancin, the reasons should be discussed and advice to practice clearly given. The applicant should also present data on the use of E-test methodology.

With regard to the first question, the applicant has outlined various ways of determining the MIC values of dalbavancin in the light of observation that under certain circumstances variability in recorded MIC values are obtained. The use of a small amount of a wetting agent P-80 is recommended. The effects of this addition are reviewed and conclusions drawn; i.e. 0,002% P-80 should be added for fresh and frozen panels but can be omitted from dry-format panels. The documentation for the measures suggested is acceptable.

As for the second one, it is argued that the compound as being a large peptide molecule thus is prone to present a problem for the use of disk diffusion assays for sensitivity testing. The applicant suggests instead the use of E-test in which the compound is applied to a test strip in a gradient fashion thus circumventing the diffusion problems inherent to dalbavancin. This is accepted.

Baseline isolates in clinical trials

Most of the microbiological data below discussed corresponds to the baseline pathogens isolated in clinical trials VER001-9 (pivotal trial, dalbavancin vs. linezolid in patients with complicated skin and soft tissue infections), VER001-16 (dalbavancin vs. vancomycin in patients with complicated and uncomplicated skin and soft tissue infections) and VER001-8 (dalbavancin vs. cefazolin in patients with uncomplicated skin and soft tissue infections). Two other clinical trials have been submitted, i.e. VER001-5 (phase 2 study, two doses of dalbavancin vs. comparator) and VER01-4 (two doses of dalbavancin vs. vancomycin in patients with catheter-related bloodstream infection, CR-BSI).

Table below shows a comparative distribution of the principal pathogens in the phase 3 studies.

Table 4. Comparative Distribution of Principal Pathogens in Efficacy Studies VER001-9, VER001-16 and VER001-8

	VER001-9 cSSSI		VER001-16 cSSSI or uSSSI		VER001-8 uSSSI	
	Dalbavancin	**Linezolid**	**Dalbavancin**	**Vancomycin**	**Dalbavancin**	**Cefazolin**
Micro ITT population	**N = 391**	**N = 215**	**N = 76**	**N = 35**	**N = 260**	**N = 112**
S. aureus: all	318 (81)	174 (81)	69 (91)	31 (89)	189 (73)	86 (77)
MRSA	181 (46)	97 (45)	55 (72)	22 (63)	51 (20)	17 (15)
S. pyogenes	19 (5)	12 (6)	2 (3)	0 (0)	36 (14)	12 (11)
S. agalactiae	16 (4)	10 (5)	2 (3)	1 (3)	11 (4)	7 (6)
Streptococcus Group G	10 (3)	6 (3)	1 (1)	0 (0)	8 (3)	4 (4)
Viridans Streptococcus	15 (4)	6 (3)	2 (3)	2 (6)	8 (3)	1 (1)
S. dysgalactiae/ Group C	6 (2)	3 (1)	0 (0)	1 (3)	3 (1)	0 (0)
ME at TOC population	**N = 301**	**N = 172**	**N = 60**	**N = 22**	**N = 173**	**N = 83**
S. aureus: all	250 (83)	141 (82)	54 (90)	18 (82)	121 (70)	63 (76)
MRSA	146 (49)	73 (42)	42 (70)	11 (50)	0 (0)	0 (0)
S. pyogenes	13 (4)	8 (5)	2 (3)	0 (0)	27 (16)	9 (11)
S. agalactiae	10 (3)	6 (4)	1 (2)	1 (5)	9 (5)	5 (6)
Streptococcus Group G	7 (2)	6 (4)	1 (2)	0 (0)	6 (4)	3 (4)
Viridans Streptococcus	10 (3)	6 (4)	2 (3)	2 (9)	4 (3)	1 (1)
S. dysgalactiae/ Group C	6 (2)	2 (1)	0 (0)	1 (5)	3 (2)	0 (0)

Source: VER001-9 CSR (Table 1.9.2); VER001-8 CSR (Table 1.9.2); VER001-16 CSR (Table 1.9.2).

S. aureus (including a high proportion of MRSA) was the most frequently isolated pathogen. In the Micro ITT and ME at TOC efficacy populations, this was present in >80% of patients in all treatment groups in studies VER001-9 and VER001-16 and by ≥70% of patients in Study VER001-8. This high rate of isolation of MRSA was not driven for the study designs except for trial VER001-16. Approximately, 35% (137/391) of patients in study VER001-9 had methicillin-susceptible *S. aureus* (MSSA) at baseline. The applicant is asked to give an overview about the origin of the *S. aureus* strains (community or hospital acquired) and the respective susceptibility towards other antibiotics. Furthermore, clinical, by-pathogen and by-patient responses at TOC confined to patients with MSSA isolated at baseline should be presented by study and discussed for dalbavancin and comparators. The requested information has been provided:

- Origin of the *S. aureus* strains (community or hospital acquired): in their response the Applicant has clarified that based on retrospective testing for pvl and the SCCmec type IV genes approximately 64% of the MRSA baseline isolates in study VER001-9 were community-acquired. This unexpected high rate of MRSA seems to be due to the fact that, in retrospect, the study was conducted during an ongoing epidemic of MRSA in North America, where a significant proportion (86.5%) of subjects were enrolled. Unlike traditional nosocomial isolates of MRSA, the community strains are usually susceptible to non-b-lactam antibiotics such as doxycycline, clindamycin and trimethoprim/sulfamethoxazole. Based on the MIC data provided in the original dossier the MRSA isolates of study VER001-9 have reduced susceptibility to tetracycline (EUCAST breakpoints for *Staphylococcus* spp.) and are susceptible to trimethoprim/sulfamethoxazole (CLSI breakpoints for Staphylococcus spp.). Apparently clindamycin has not been tested against these MRSA isolates. The Applicant should further address this issue, i.e. whether clindamycin has been tested against MRSA isolates and if this is the case then MIC50, MIC 90 and MIC range should be provided as well as whether these strains wee D-test positive or negative.

- Clinical and microbiological success rates for MSSA do not substantially differ from those observed in the whole set of all *S. aureus* and in the subset of MRSA.

Because *S. aureus* is a frequent inhabitant of cutaneous flora, the type and the quality of the samples performed are crucial. Some precisions on the technical methods used (surgical samples, needle aspirations, etc.) in the pivotal study (VER001-9) should be given by the Applicant. It has been clarified that most of the samples were obtained by deep swap. Although biopsy or needle aspirations are considered better methods from a microbiology point of view, deep swab is also considered acceptable for "open" wounds. It is assumed that for cellulitis, samples were obtained by needle aspiration.

S. pyogenes was the second most frequent baseline pathogen overall, although at a small number. Smaller numbers of other beta-haemolytic and viridans streptococci and occasional Gram-positive anaerobes were encountered. The low number of baseline streptococci in the trials raises concerns about the demonstration of efficacy against these microorganisms. The Applicant's proposal, i.e. adding an asterisk to *S. pyogenes* and *S. agalactiae* is not endorsed. However, based on the in vitro data their listing in section 5.1 (category 1) can be accepted (please note that questions have been posed on the *in vitro* activity of dalbavancin against streptococci).

Enterococci and coagulase-negative staphylococci were considered to be potential contaminants and were not included in efficacy analyses. The role of enterococci as colonizers has been discussed and acknowledged for other previously approved antibacterials intended to treat the same kind of infections. Coagulase-negative staphylococci (CoNS) are common colonizers of the human skin. They are increasingly recognized as agents of clinically significant nosocomial bloodstream infections, although *S. epidermidis* has been involved in soft and tissue infections, mainly in presence of permanent intravascular catheters and in surgical wounds in ICU patients (e.g. patients that underwent cardiac surgery).

In spite of this enterococci and staphylococci are included within the list of commonly susceptible species in section 5.1 of the SPC. This is not endorsed. Enterococci should not be listed in section 5.1. As for CoNS, *in vitro* data submitted for them is considered supportive. Indirect prove of the in vivo efficacy of dalbavancin against CoNS can be ascertained from trial VER001-4, in patients with catheter-related blood stream infections. Taking all this into consideration it is believed that CoNS can be listed in section 5.1, although no asterisk (denoting clinical efficacy) should be added.

Within each study a very small number of patients were found to have a blood pathogen, e.g. in study VER001-9, in the Micro ITT population, 12 patients (3.4%) in the dalbavancin group and 6 patients (3.1%) in the linezolid group were bacteremic with a Gram-positive pathogen at baseline. *S. aureus* was the Gram-positive pathogen isolated from a baseline blood culture for 11/18 (61.1%) patients. Of the 11 *S. aureus* isolates obtained from blood samples at baseline, 6 (54.5%) were MRSA. Other pathogens included *S. agalactiae* (3), *S. pyogenes* (2), *Streptococcus* group G (1) and *Streptococcus* group C (1). The lack of experience in patients with bacteremia should be explicitly mentioned in section 4.4 of the SPC. This has been done in the latest SPC proposal.

The MIC distributions for *S. aureus* (MSSA and MRSA) and *Streptococci* spp. (other than *S. pneumoniae*) in phase 3 clinical trials ranged from 0.03 to 0.25 mg/L and from 0.03 to 0.06 mg/L, respectively. In the phase 3 studies there was no apparent correlation between success, whether clinical or microbiological, and MICs. However, as the Applicant's states, the dalbavancin MIC distributions were very narrow, precluding the prediction of successful microbiological outcome by MIC.

Pharmacodynamic data leading to selection of the dosing regimen

Dalbavancin has been tested in several animal models of infection including acute septicaemia, and in several models in which the primary endpoint was bacterial load in the infected site or tissue (endocarditis, pneumonia, granuloma pouch, and prophylaxis of foreign body infection). Most of the experiments targeted *S. aureus*, in particular MRSA.

In vivo PK/PD relationship of dalbavancin was investigated using the thigh infection model in neutropenic mice, using *S. pneumoniae* and *S. aureus*. Dalbavancin produced *in vivo* bactericidal activity against both bacteria and its efficacy was dose-dependent.

In the single dose study, against *S. aureus* strain ATCC 29213 only the two highest doses (40 mg/kg and 80 mg/kg) resulted in the killing of *S. aureus*. Certain degree of regrowth was seen at 20 and 40 mg/kg over the 96 hour period. Dalbavancin plasma levels were determined with a microbiological assay with *Bacillus subtilus* as the test organism. In the dose fractionation study, the two highest total doses were effective with all dosage intervals; however, net reduction in CFU/thigh (1->2 log10 CFU/thigh) was greatest when larger amounts were given less frequently (q 36 or 72 h). The PK/PD parameter that best correlated with efficacy for *S. aureus* was the 24-h AUC/MIC ratio. To determine if the free 24-h AUC/MIC (f24AUC/MIC) required for a particular effect (static, 1-log killing etc.) was similar for multiple pathogens, the activities of the q24h and q72h dosing regimens of dalbavancin against six strains of *S. aureus* were studied. The "static" mean f24AUC/MIC ratio (SD) for all strains of *S. aureus* tested was 265 (143) for the q24h regimen and 160 (67) for the q72h. Although it is stated that, in general, the shape of the dose-response curves was similar for all strains when the values of the PK/PD index for individual strains are seen differences are observed. No very much emphasis has been made in this report on the data on *S. pneumoniae* as it is not considered relevant for the claimed indication but a finding that deserves to be mentioned is that for *S. pneumoniae* less drug is needed to achieve similar endpoints.

In the view of the CHMP other parameters such as Cmax/MIC are as well good predictors of response. Time over MIC is also considered by the Applicant, however it was found to be a poor predictor of efficacy. In the view of the CHMP this is likely to be due to the fact that in most cases plasma concentrations remained above MIC values during the sampling time. Correlation between Cmin (a highly variable parameter as for the data provided) and efficacy has not been explored.

In summary, the dose-response relationships in this study support the use of large infrequent doses to optimize *in vivo* treatment efficacy. This fact has been taken on board when designing the dosage regimen for the clinical development.

Further support is given from study VER001-2 (healthy volunteers) that showed prolonged bactericidal activity (up to 7 days) in serum after administration of 500 mg and higher single doses dalbavancin. As previously stated, in phase 2 and 3 studies no attempt has been made to correlate clinical response with Cmax/MIC, AUC/MIC or time T > MIC. Admittedly, the fact that only 1 dose schedule was evaluated in most of these studies and the high response rates may limit the usefulness of this exercise, but having these data might be of some help. In this regard, the Applicant could provide, as an example, an assessment of the correlation between drug levels at 14 days and cure and eradication rates. A logistic regression model assessing the relationship between AUC/MIC and clinical and eradication responses at EOT and TOC in the ME could be an example. The Applicant has not provided the requested analysis. However, the box plot submitted seems to show that the median concentration of the failure group is below the median of the success group. This is not reassuring but is based on a low number of patients. The Applicant reasoning in support of the conclusion that performing the PK/PD analysis may not provide any additional information is somehow expected as this analysis would not be sufficiently discriminative due to the low rate of failures, the narrow MIC distribution and the fact that there is a single dosage regimen tested.

A Monte Carlo analysis (rather than a truly PK/PD relationship analysis) was performed to confirm the dosage used in patient studies and to quantify the therapeutic window relative to MIC with the proposed dose regimen, using both time-dependent (t > MIC) and concentration-dependent (the free drug AUC/MIC) parameters. In the mouse neutropenic thigh infection model, *S. pneumoniae* strains were inhibited and/or killed by lower dosages of dalbavancin compared to *S. aureus*, reflective of the relative MICs. Based on this model, the AUC/MIC target was 10-fold lower for *S. pneumoniae*. Target attainments based on AUC14Day/MIC were three dilutions higher for *Streptococcus* spp.

The Monte Carlo simulations were based on *S. pneumoniae* as a representative of streptococci. Among the *Streptococcus* spp, *S. pyogenes* is considered to be the most relevant baseline pathogen for SSTIs while *S. pneumoniae* is known to rarely cause SSTIs. As a consequence, the lack of a Monte Carlo simulation for *S. pyogenes* should be justified. The Applicant's response has not provided further information on this issue. Overall, it is felt that the knowledge of dalbavancin pharmacodynamics against *S. pyogenes* is scarce as it seems to be limited to MIC, MBC and one time kill study.

Comparative data are available for dalbavancin compared with penicillin only in static conditions (comparative MICs and MBCs). No strains of *S. pyogenes* have tested in the neutropenic murine thigh model and the Monte Carlo simulations did not include this species. However, the following considerations have been taken into account to consider this issue solved:

- *S. pyogenes* is listed as susceptible in section 5.1 based on the MIC data provided.
- No asterisk is added to denote clinical efficacy due to the low number of isolates in the pivotal trial.
- The Rapporteurs agreed on setting the same breakpoints (see below) for both Staphylococci and Streptococci.

The susceptibility breakpoints for dalbavancin, presented for consideration in Section 5.1 of the proposed SPC, are as follows: Susceptible ≤1 mg/L and Resistant >1 mg/L for staphylococci, and Susceptible ≤2 mg/L and Resistant >2 mg/L for streptococci. The basis of the proposed breakpoints needs to be explained as it is not easy to see the reasons for setting different breakpoints for *S. aureus* and streptococci. It is claimed that the mouse thigh infection model study supports the proposed break points for *S. aureus* and streptococci. However, the submitted background data do not seem to support the target free drug AUC/MIC ratios (1000 for *S. aureus* and 100 for *Streptococcus* spp) which were obtained from the mouse study and applied in the Monte Carlo simulations. More detailed information should be provided on the background data applied in the Monte Carlo simulations in order to define possible breakpoints as suggested to EUCAST. Besides, the applicant should explain the discrepancy between the statement that "Streptococci are more susceptible to dalbavancin than *S. aureus* and required lower doses for bactericidal effect" and the fact that the breakpoint proposed for streptococci is higher than that for *S. aureus* (2 mg/L and 1 mg/L, respectively). The impact of PAE on the suggested breakpoints should also be commented upon. As previously stated this aspect should be observed as a part of post-marketing program in order to investigate the possibility of resistance development.

The Applicant agreed to discuss the MIC breakpoints in the context of the EUCAST process. At the EUCAST meeting on January 28th 2008, the Rapporteurs agreed with EUCAST on the following breakpoints:

Staphylococci: S≤0.25 mg/l and R>0.25 mg/l (Applicant's initial proposal 1/1)
Streptococci: S≤0.25 mg/l and R>0.25 mg/l (Applicant's initial proposal 2/2)
S. pneumoniae: IE (not requested)
Enterococci: IE (not requested)
Non-species related breakpoints: IE

The applicant argues that in the mouse thigh study therapeutic success was achieved by the use of lower dosage for streptococci compared to staphylococci. Thus, streptococci are more within therapeutic reach than staphylococci. The Applicant's reasoning is not completely endorsed. However, at the EUCAST meeting on January 28th 2008, the Rapporteurs agreed on setting the same breakpoints (see above) for both *Staphylococci* and *Streptococci* and, consequently, provided that the Applicant makes appropriate changes in the SPC this issue is considered solved.

Pharmacodynamic aspects relevant to safety
Very preliminary data has been submitted with regard to the potential of dalbavancin to select resistant microorganisms in the normal flora. From this data it seems clear that vancomycin-resistant enterococci can be selected. Another potential concern is the overgrowth of gram-negative bacilli. As the majority of administered dalbavancin is eliminated unchanged, and the half life is long, possible influences upon extra-human bacterial ecosystem should be discussed as well as the risk of establishing resistant strains of potential human pathogens.

The submitted data is not considered adequate to evaluate this issue. It seems that the applicant has not submitted all data from the study VER001-15 which were supposed to be obtained according to the protocol. The remaining data for all 12 individuals at all occasions and on all media tested should be

provided. In addition, the applicant's response based upon the data from VER001-15 is of little, if any relevance for the present situation in Europe. The applicant should provide a more updated evaluation of the present situation of the glycopeptide resistance in Europe, including the problem regarding GRE present in the sewage water.

Due to the deficiencies in study VER001-15, it is considered that there is an unknown but potentially problematic risk of resistance development both in vivo and in extra-human eco-systems. Particular concern is the possibility that use of dalbavancin might promote the emergence of glycopeptide resistant enterococci.

Other pharmacodynamic aspects relevant to safety are discussed in the safety section.

There are no clinical data regarding pharmacodynamic interactions. Checkerboard studies did not show antagonistc interactions. *In vitro*, synergy between dalbavancin and oxacillin was observed against a number of strains of staphylococci. The possible mechanism(s) behind the *in vitro* synergy observed should be described. In addition, the possible clinical impact if appropriate should be addressed. The Applicant in their response has clarified that the existence of a mechanism for a synergy between dalbavancin and oxacillin is not known. The submitted documentation does not support a synergy or add any new information on this issue, but since such a mechanism is not referred to in the SPC, it does not seem to be a point to pursue this question.

Clinical efficacy

The phase 2/3 clinical programme of dalbavacin includes one phase 2 study in patients with the claimed indication, i.e. complicated skin and soft tissue infections (cSSTI) in adults (study VER001-05), and one phase 3 pivotal study in cSSTI (VER001-9). In addition 3 supportive studies are presented: an open study in complicated or uncomplicated SSTI known or suspected to be due to MRSA (VER001-16), a study in uSSTI (VER001-8) and a phase 2 study in patients with catheter-related bloodstream infections (CRBSI). An overview of these studies is provided in the table below.

Study ID/ Type	**No. Study Centres/ locations**	**Study design/ objective**	**Dalbavancin dose/ duration**	**Comparator**	**No. subjects treated (Dalbavancin / comparator)**
VER001-5 Phase 2 study in cSSTI	10 sites in the US	Randomized, open-label study to evaluate efficacy, safety and tolerability of 2 dose regimens of dalbavancin relative to standard therapy in cSSTI	Study arm 1: IV dalbavancin: 1100mg (single dose) on Day 1 Study arm 2: IV dalbavancin: 1000mg on Day 1, 500mg on Day 8.	Standard antibiotic therapy: as defined by investigator prior to randomization	62 in total Study Arm 1: 20 Study Arm 2: 21 Study Arm 3: 21
VER001-9 Phase 3, pivotal study in cSSTI	65 sites in Canada, Estonia, Germany, Latvia, Lithuania, UK and US	Randomized, double-blind study to assess the noninferiority of dalbavancin relative to linezolid in the treatment of cSSTI with suspected or confirmed Gram-positive bacterial pathogens requiring parenteral therapy	IV Dalbavancin: 1000mg on Day 1, 500mg on Day 8, possible switch to oral placebo q12. Treatment duration: 14 days.	IV linezolid: 600mg q12h, possible switch to oral linezolid 600mg q12h. Treatment duration: 14 days.	854 in total (571/ 283)
VER001-16 Phase 3 study in cSSTI or uSSTI	22 sites in Canada and the US	Randomized, open-label study to compare dalbavancin and vancomycin in the treatment of cSSTI or uSSTI with suspected or confirmed MRSA	IV dalbavancin: 1000mg on Day1, 500mg on Day 8 (optional for uSSTI).	IV vancomycin: 1000mg q12h; after 24 hours parenteral therapy possible switch to oral cephalexin 500mg	156 total (107/ 49)

				q6h if pathogen was susceptible. Treatment duration: 14 days.	
VER001-8 Phase 3 study in uSSTI	70 sites in Canada, Estonia, Germany, Italy, Latvia, UK and US	Randomized, double-blind study to compare dalbavancin and cefazolin in the treatment of uSSTI	IV dalbavancin: 1000mg on Day 1, with the option to follow 500mg on day 8, possible switch to oral placebo q6h.	IV cefazolin: 500mg q8h, possible switch to oral cephalexin 500mg q6h. Treatment duration: 7 or 14 days	553 in total (367/ 186)
VER001-4 Phase 2 study in CRBSI	13 sites in the US	Randomized, open-label study to evaluate efficacy and safety of dalbavancin relative to vancomycin in the treatment of CRBSI with suspected or confirmed Gram-positive bacterial pathogens.	Study arm 1: Weekly IV Dalbavancin: 1000 mg on Day 1, 500 mg on Day 8. Study arm 2: Daily IV Dalbavancin: 650 mg on Day 1, 65 mg on Days 2-14 (this arm was discontinued).	IV Vancomycin: 1000 mg q12h, or dose-adjusted for renal impairment. Could switch to IV nafcillin or oxacillin 2 g q4h or q6h after pathogen identification and susceptibility testing.	53 total Study arm 1: 23 Study arm 2: 2 Study arm 3: 28

No formal dose finding program has been submitted. The rationale for the dosage regimen chosen for the phase 3 pivotal study VER001-9 (1000 mg on day 1 followed by 500 mg on day 8) is based on 1) the observation of bactericidal activity in plasma of healthy volunteers after a single dose of dalbavancin, that were maintained over time; 2) the neutropenic murine thigh infection model that lead to the observation that higher doses spaced over time were more effective than lower doses administered more frequently; 3) a Monte Carlo simulation (rather than a formal PK/PD model) was performed to estimate the percentage of attainment of several PK/PD indices; and 4) Study VER001-5 compared two doses of dalbavancin, i.e. 1110 mg as a single dose on day 1 vs. 1000 mg on day 1 followed by 500 mg on day 8. Sixty-two patients received at least one dose of study medication (Study Arm 1: 20; Study Arm 2: 21; comparator antibiotic: 21). It was concluded that patients receiving the proposed dosage had higher success rates (94.1%) than patients in Study Arm 1 (61.5%) or comparator (76.2%).

In the phase 2/3 studies a diversity of comparators were used, i.e. linezolid (pivotal study), cefazolin and vancomycin. Moreover, in some of these studies switch to oral antibiotics such as cefalexin and semi-synthetic penicillins was permitted. In addition, some of the studies also included patients with uncomplicated skin and soft tissue infections. As a consequence, they are described separately.

Study VER001-9 (pivotal)
VER001-9 was a randomised, double-blind (third party unblinded), multi-centre study conducted in the USA and Europe. The primary objective of the study was to compare the safety and to demonstrate the equivalent efficacy of dalbavancin to that of linezolid in the treatment of adults with complicated SSTI due to Gram-positive bacteria. The primary endpoint was the Clinical Response Rate in the Clinically Evaluable (CE) patient population at the Test-Of-Cure (TOC) evaluation. Dalbavancin was to be considered non-inferior to the comparator linezolid if the lower margin of the confidence interval for the difference in success rates between treatment groups was above 12.5%. Linezolid was questioned by the CHMP as the comparator of choice in this clinical setting, since the standard treatment of non-MRSA cSSTIs would be a β-lactam. However, considering that a relevant percentage of patients included in study VER001-9, had MRSA infection (many of them CA-MRSA), linezolid is considered to be an acceptable comparator. In the light of the actual results of the study, the discussion on the acceptability of a priory defined marging of non-inferiority becomes of secondary importance, but a delta of 10% should be used when interpreting the data.

Patients assigned to dalbavancin received a 1000 mg dose on Day 1 followed by a 500 mg dose on Day 8. Patients assigned to linezolid received IV linezolid 600 mg q 12 h, with a possible switch to

oral linezolid 600 mg q 12 h after at least 24 hours of parenteral therapy, provided that they met predefined criteria for switching, i.e. defervescence or improvement in the clinical signs of infection the SSTI site.

Linezolid was used as the sole comparative therapy although it is not considered as standard therapy for treating cSSTI. The choice of this over vancomycin for MRSA infections and over semi-synthetic penicillins is questioned and should be further justified.
Key inclusion and exclusion criteria were as follows:

Inclusion criteria	
• Patients with an infection consistent with complicated SSSI defined as infection involving deeper soft tissue or requiring significant surgical intervention. Such infections included:	• Major abscesses; • Major burn (≤20% body surface area); • Traumatic wound infection; • Deep skin/skin structure infection such as extensive/ulcerating cellulitis (i.e., involved deep subcutaneous tissues, was phlegmonous, or required surgical debridement); • Surgical wound infection; • Other deep soft tissue infection; • SSSI known or suspected to be caused by MRSA;
• Patients expected to require at least 24 hours of parenteral therapy for suspected Gram-positive complicated SSSI	
• Patients with at least two of the following signs and symptoms of complicated SSSI:	• Drainage/discharge; • Erythema; • Fluctuance; • Heat/localized warmth; • Pain/tenderness to palpation; • Swelling/induration;
• Patients with at least one of the following signs of systemic infection/complicating factor:	• Increased temperature (≥100.5°F [≥38.1°C] measured orally or its equivalent measured by another method); • Increased WBC (>10,000/mm3) • Bandemia (>10% bands regardless of total peripheral white count); • Other complicating factor as determined by the investigator. (Other complicating factors included reasons such as a history or suspicion of MRSA or mixed infection, diabetes mellitus, obesity, prior antibiotic failure, and infection severity that warranted parenteral antibiotic therapy).

Exclusion criteria
• Known creatinine clearance ≤50 mL/min
• Known bilirubin >2x the upper limit of normal (ULN)
• Received greater than 24 hours of a systemic antibiotic with a Gram-positive spectrum of activity within 7 days of study medication initiation, unless the patient was deemed a failure (i.e., the clinical site was worse after >72 hours of therapy or a Gram-positive pathogen had been isolated that was resistant to current therapy)
• Known or suspected to have osteomyelitis or septic arthritis
• Infections complicated by the presence of prosthetic materials that would not be removed such as permanent cardiac pacemaker battery packs, or those involving joint replacement prosthesis
• Self-limited infections such as isolated folliculitis and isolated furuncles or other infections that have a high cure rate after surgical incision alone
• Patients who have had more than two surgical interventions (defined as surgery that cannot be performed at the bedside) for the SSSI
• Patients expected to need more than two surgical interventions during the study (defined as surgery that cannot be performed at the bedside) for the SSSI
• Skin and skin structure infection: • With arterial insufficiency, such as deep diabetic foot ulcers, decubitus ulcers, and ischemic ulcers; • Necrotizing fasciitis, gas gangrene; • Burns on greater than 20% of total body surface;
• Superinfected eczema or other chronic medical conditions (i.e., atopic dermatitis) for which inflammation may be prominent for an extended period even after successful bacterial eradication
• Anticipated need for prolonged antibiotic therapy (i.e., >14 days)
• Neutropenia defined as an absolute neutrophil count <500/mm3
• Receiving chronic immunosuppressive drugs, including prednisolone >40 mg/day (or equivalent)
• CD4 count known at the time of enrollment to be <200/µL

• Causative organism (if known at enrollment) with documented resistance or intermediate sensitivity to vancomycin or linezolid

The primary efficacy variable was the clinical response at the test-of-cure (TOC) assessment for the clinically evaluable (CE) population. Clinical response was categorised as success, failure and indeterminate. Indeterminate outcomes were to be included as failures in the ITT analysis. One of the definitions of indeterminate response was "other"; which is a highly unspecific term and considered unacceptable. The applicant clarified that "indeterminate" was not to be used for instances in which making a clinical judgement is difficult. Moreover, the low number of "indeterminate" outcome makes unlikely this to have a relevan impact on the study results.

The *primary* endpoint was *Success* defined as sufficient resolution of the local and systemic signs and symptoms of SSTI such that the patient did not receive new systemic antibacterial treatment for SSTI. This implies that complete resolution of symptoms together with improvement is combined in the definition. Separate analysis of the true cure rates and improved rates at the TOC visit were requested. The Applicant argues that success was defined as sufficient resolution such that further systemic antibacterial treatment for the SSTI was not required. The CHMP agrees that for some patients local signs might persist even after it has been considered that there is no need for continued antibacterial treatment, but this is not the case for all patients, i.e. it is expected that for several patients the infection would be cured. It is somewhat surprising that sufficient information has not been included in the CRFs to decide for each patient if the infection has been cured or has improved. It is therefore not accepted that is should be impossible to define true cure rates for this patient population, as has indeed been provided for other studies in this indication. However, on inspection of the CRF it is clear that sufficient information was not asked for, and therefore this issue is probably not possible to solve by the data collected in this study.

The very long elimination half-life of dalbavancin caused some difficulties with the timing of the TOC. At this visit there should be no or minimal levels of active drug remaining at the body site or in body fluids pertaining to the indication sought (as discussed in the CHMP Note for Guidance). It could be discussed whether the TOC visit actually should have been scheduled at a later time point to ascertain adequately low levels of dalbavancin. On the other hand, taking into consideration the much shorter t1/2 (mean 5-7 hours) of linezolid, timing the visit too late would not be unproblematic either.

The LFU was added to the protocol through Amendment 1 (May 2003) and the rationale behind this was to collect information about possible late relapses/recurrences (to capture post TOC outcome information on recurring signs and symptoms of SSTI). The LFU measurements could have been valuable to help overcome the problems related to the TOC visit. However, one could question whether a phone call assessment would be as reliable as a physical visit. Furthermore, the late inclusion of this visit in the protocol implies that several patients would not be a part of this procedure as they were enrolled before the amendment came into operation. It seems that a total of 592 patients in the CE population at TOC were deemed Successes and thereby should have been followed up. However, only 479 patients were contacted for a LFU, hence this presumable means that 113 patients were not assessed at LFU.

An analysis of the frequency distributions of EOT and TOC visits was performed and the visit windows was expanded, both in accordance with the Statistical Analysis Plan. Given the discussion regarding the importance of the timing of the TOC visit; it seems however, strange to allow for an open ended window. However, sensitivity analyses provided by the Applicant did not show a relevant interference of this fact on the final study results.

Relevant secondary efficacy variables were clinical response in the ITT population at TOC, clinical response in the CE and ITT populations at end of therapy (EOT), by-patient and by-pathogen microbiological response in the Micro ITT and ME populations at EOT and TOC assessments and clinical response at late follow-up (LFU, phone interview) for the ITT and CE populations, in patients who were clinical successes at TOC to determine relapse of SSTI.

Outcomes:

A total of 873 patients were randomised to study treatment, and 749 completed therapy; 496 in the dalbavancin group and 253 in the linezolid group. Of the 854 patients who received at least one dose of study medication, 147 patients discontinued study medication prematurely (104 in the dalbavancin group and 43 in the linezolid group). The most frequent reason for discontinuation was dispensing errors that led to inadvertent premature discontinuation of study medication, and withdrawals requested by personnel not associated with the study (e.g., surgical team, infectious disease team, etc.). Adverse events were the second most frequent reason for discontinuing therapy (in total 32 patients; 23 in the dalbavancin group and 9 in the linezolid group). AEs leading to withdrawal were considered related to treatment for 8 patients in the dalbavancin arm and 5 in the linezolid arm. The most frequent reason for withdrawal from the study as a whole, i.e., non-completion of the TOC study visit irrespective of study medication completion, was lost to follow-up (comprised in total 66 patients; 44 in the dalbavancin group and 22 in the linezolid group).

The clinically evaluable (CE) population at TOC included 660 patients, 434 in the dalbavancin group and 226 in the linezolid group. The microbiological intent-to-treat population (Micro ITT, i.e. all patients in the ITT-population who had at least one Gram-positive pathogen present at baseline) at TOC consisted of 550 subjects, 358 subjects in the dalbavancin group and 192 in the linezolid group. The microbiologically evaluable population at TOC comprised 429 patients, 277 in the dalbavancin group and 152 in the linezolid group.

The use of two different CE populations and the inclusion of patients in the CE population (at TOC) who did not attend the EOT visit are not considered appropriate. A CE population should include only patients for whom there are data from all scheduled visits. In addition, it is noted in the flow charts submitted that there is a strikingly high proportion of dalbavancin treated patients who did not satisfy the CE criteria (98 vs 34 in the comparator group). At this stage it cannot be excluded that this is related to a lack of efficacy.

Concomitant antibiotic therapy permitted in the protocol was aztreonam and/or metronidazol. Apparently, 12% of patients in each treatment group received concomitant antibacterial therapy that was considered violations of protocol.

Demographic characteristics were similar between the treatment groups. In the CE population, 60.8% of the patients were male in the dalbavancin group and 61.9% in the linezolid group. The more frequent ethnic origin was Caucasian (67.7% in the dalbavancin group and 69% in the linezolid group), followed by Hispanic/Latino (20.3% in the dalbavancin group and 16.4% in the linezolid group). Approximately, 10% of patients were black in both treatment groups. Mean creatinine clearance was 130.6 ml/min in the dalbavancin group and 128.6 ml/min in the linezolid group. Approximately 60% of patients were hospitalized at study entry in the dalbavancin group and 62% in the linezolid group. Median time to switch to oral was just 2 days.

Regarding the presence of risk factors for SSTI, 24.3% dalbavancin-treated patients (ITT population) and 21.2% linezolid-treated patients presented diabetes mellitus and 10.7% dalbavancin-treated patients and 6.4% linezolid-treated patients presented vascular disease.

Though it is stated that the selection criteria define a population with cSSSI, the CHMP identified a number of aspects precluding to reach such conclusion:

- Firstly, the inclusion criteria did not require the presence of at least 1 sign of systemic infections, as the list also included the highly unspecific “other complicating factor”. In addition, the requirement that 2 of 6 listed signs and symptoms of complicated SSTI must be present was not considered adequate. Furthermore, approximately 25-30% of the patients neither had fever, leucocytosis or bandemia. Similarly, many of those patients did not have any other systemic sign of infections which should allow for inclusion. A definition and characterisation of the severity of the infection could not be found, making it difficult to determine how many patients enrolled at baseline could be characterised as having severe infection and were in actual need of i.v. antibiotic treatment. The cut off of 24 hours regarding the presumed need for IV therapy was deemed rather soft and questionable as indicator of

cSSSI. Indeed, median time to switch to oral was just 2 days, thus suggesting a majority of patients were close to the mild spectrum of the disease. Furthermore, only 539 (63.1%) patients were hospitalised at study entry (62.5% in the dalbavancin group and 64.3 % in the linezolid group).

- The number of patients with complicating factors was low, i.e. patients with diabetes mellitus and with peripheral vascular disease represent only 23% and 9%, respectively, of the enrolled population (CE population). In addition, only 12 (3.4%) dalbavancin-treated patients and 6 (3.1%) linezolid-treated patients were bacteremic at baseline.

Overall, the patient population was deemed mostly representative of the less severe end of the disease and the need for intravenous therapy should be further substantiated. Consequently, the Applicant was requested to further ensure that patients enrolled in study VER001-9 had in fact complicated infections and additionally that they were in need of intravenous therapy due to the severity of the disease. The Applicant argues in their response that "complicated skin and soft tissue infections" are not a universally-defined clinical entity, but are most often used in a regulatory context and specifically refers to a regulatory definition set up in a draft FDA guidance for industry. In the CHMP's view, the fact that a skin and soft tissue infection qualifies as complicated does not necessarily mean that the patient is in need of antibiotic treatment and in particular of an antibiotic administered intravenously. In addition, according to the "regulatory" definition, in the majority of cases the qualifying criterion was "deep tissue involvement", which can be regarded as a rather subjective criterion. Importantly, no surgical intervention was anticipated in the majority of cases. Furthermore, being major abscess the main clinical diagnosis it is surprising that only 30% of patients with abscesses underwent surgical drainage. It is also striking that for patients with uncomplicated SSTI in studies VER001-16 and VER001-8 the most common categories of infection were also abscesses not requiring intra-operative surgical drainage and cellulitis. In summary, key factors defining cSSTI such as need for surgical intervention and underlying disease appear to be uncommon in the enrolled population. The total number of patients that underwent surgical intervention should be provided with independence of the clinical diagnosis and split by geographical region (Europe vs. North America). An adequate explanation about the low rate of incision and drainage in the case of abscesses should be given. Furthermore, the differences between major abscesses and abscesses not requiring intra-operative surgical drainage (inclusion criterion used in patients with complicated and uncomplicated SSTIs) should be provided.

The inclusion of patients with major burns (≤20% body surface area) does not seems entirely appropriate given the fact that infected burns behave differently, need different baseline care, and last longer than the other lesions. Given the low number of patients with such infections included, and the fact that they were all classified as success at TOC, they are not considered in any considerable degree to have influenced to results of the study. Immunodepressed patients, patients with known or suspected osteomyelitis or septic arthritis, SSTI with arterial insufficiency (such as deep diabetic foot ulcers, decubitus ulcers, and ischemic ulcers), necrotizing fasciitis, gas gangrene and burns involving > 20% of body surface were excluded. Similarly, patients with known creatinine clearance ≤ 50 ml/min and known bilirubin > 2x ULN were excluded from the pivotal study. Due to the double blind nature of the study and the difficulties in blinding the necessary dose adjustments in these patients it is deemed acceptable. Overall, the limitations of the clinical database should be reflected in section 4.4 of the SPC.

The Applicant was requested to analyse the primary efficacy data for different degrees of severity, which was deemed essential to further assess whether the enrolled population was nor not representative of the target one. According to the data provided, the Applicant states that more than 96% of patients overall had a systemic sign of infection (WBC > 10000; Bandaemia > 10% or fever > 100.5 F) or another complicating feature, as per the enrolment criteria. However, when only systemic signs are considered, figures are 381 (66.7%) and 201 (71.0%), respectively. The number of patients with "other complicating factor" is 187 on dalbavancin and 74 on linezolid. Apparently, some patients had more than one complicating factor present. The most common reason listed as "other complicating factor" in this population was "Suspected or known MRSA infection". 64% of all of the MRSA isolates were community-acquired. Even acknowledging that CA-MRSA could be associated with

more serious infections it should not per se be interpreted as an argument for the infections to be on the more severe end of disease. The crucial criteria for the diagnosis of a severe infection in a patient are the clinical symptoms, i.e. the presence of systemic signs of infection, and the presence of comorbidities, not whether or not the infection is caused by MRSA.

The Applicant has provided a post-hoc comparison (not followed by statistical analysis) of clinical and microbiological outcomes by patients with systemic signs of infection vs. those without any of these signs has been provided showing slightly differences in the outcomes, thought the results can be regarded as consistent with the overall study results.

There are some additional uncertainties regarding the inclusion / exclusion of some groups of patients. It appears that 24 subjects categorised as "Patient without at least one systemic infection / complicating factor of infection" were granted a waiver by the sponsor. The Applicant has provided additional information on these subjects, though insufficient to draw firm conclusions. Therefore, they have committed to provide further information on the reasons for granting a waiver for all 24 patients. In any case, the Applicant has conducted additional analyses in their responses that exclude these patients. Also a total of 61 (10.7%) patients in the dalbavancin group and 40 (14.1%) in the linezolid group had a Gram-negative aerobic/ anaerobic pathogen and did not receive aztreonam/metronidazol. These patients were to be excluded from the CE population. However, in the listing of patients excluded from the CE population this violation was not given as reason for exclusion by anybody in either group. However, since most of these patients had a successful outcome, it is unlikely to have impacted the study results. Finally, the decision to include those patients (n=90) in the CE who had growth of a pathogen despite receiving antibiotics is not unproblematic. Samples taken from infected tissue might show growth if the antibacterial has not yet reached high enough concentration, and does not necessarily mean that the antibacterial drug was ineffective. The Applicant has not properly addressed this aspect and should provide for each of the 90 patients, information regarding the antibacterial agent administered, the dose and duration of therapy, and the species isolated from the infected site. In both treatment arms in study VER001-9, the infection was classified as "Other deep soft tissue infection" in approximately 16% of the patients. The most common infection in this group was "SSTI known or suspected to be caused by MRSA", other common infection types were cellulitis, different types of abscesses and ulcers/ulcerations. "SSTI known or suspected to be caused by MRSA" was one of the specific inclusion criteria and it is unclear why patients who fulfilled this criterion were categorised under "Other infection" instead. It also seems that some of the infection types included under this category does not qualify as cSSTI. A reclassification of "Other deep soft tissue infections" has been provided by the Applicant as per CHMP request. The investigator assigned the infection according to clinical judgement and therefore it seems impossible to reclassify the "other"-infections to specific categories, rather underlining the problem with the use of such open categories and reinforcing the convenience of a confirmatory clinical study in a well- defined population. Furthermore, it is somewhat surprising that information sufficient to do a retrospective reclassification is not available in the CRFs. It is noted that for WBC in the "other" category and for temperature for both categories the mean is below the value which would qualify for the presence of a systemic sign of infection. These are presumably baseline values, and would indicate that the patient population does not in majority consist of severely ill patients.

The Applicant states that the pharmacokinetic profile of dalbavancin, and the ADME profile of linezolid, facilitated the outpatient management of patients via OPAT. In the Applicant's view, the differences in rates of hospitalisation across the studies of dalbavancin are primarily indicative of differences in practice between the centres participating in each of the studies, rather than the severity of infection. The explanation is deemed acceptable, though these differences might difficult the extrapolability of the results to the EU setting.

The time to oral switch has been longer in other cSSTIs, but it is accepted that using this factor to compare disease severity between studies might be difficult. The arguments that the knowledge of the pharmacokinetic properties of the study medications may have influenced the investigators to consider a rapid switch to oral therapy as reasonable also seem to be relevant. However, neither of these

arguments can completely remove the concern that the rapid switch to oral therapy might be an indicator of less severe disease.

Dalbavancin was shown to be non-inferior to linezolid in terms of clinical response at TOC (CE population) using a delta of 12.5%. In the CE population response rates were 88.9% (386/434) for dalbavancin and 91.2% (206/226) for linezolid (see table below).

Clinical Response at Test of Cure (CE at TOC population)

Clinical Response	Dalbavancin (N=434)		Linezolid (N=226)		Treatment Difference (%)	95% CI
Success	386	(88.9%)	206	(91.2%)	-2.21	-7.28, 2,86
Failure	48	(11.1%)	20	(8.8%)		

The response rate of approximately 90% in the CE population seems rather high, and is similar to the response rates in study VER001-16 and 8 (see below). These studies enrolled subjects with both uSSTI and cSSTI, and uSSTI, respectively. As lower success rate in complicated infections would normally be expected, this further strengthens the concern about the validity of the study population in the pivotal trial. In addition, there seems to be marginal differences in the presence of underlying diseases, like diabetes and vascular disease, between the phase III trials. The Applicant states that the response rate is in line with previous published studies in the same indication. Admittedly, the Applicant provides a list of examples of studies with consistent cure rates. However, a number of examples with lower cure rates could have also been given. In any case, these examples highlight the variability of the response rates across studies and reinforce the need for a second pivotal trial.

In the ITT population cure rates were 76.5% (437/571) for dalbavancin vs. 82.7% (234/283) for linezolid, the lower bound of the 95%CI around the difference in cure rates being -12.03, -0.27. In other words, from a statistical point of view, dalbavancin was shown to be inferior to linezolid based on the clinical response at TOC for the ITT population. This result appears to be related to the uneven distribution of patients with indeterminate response. This imbalance is explained by the higher number of patients in the dalbavancin arm (24, 4.2%) that received <3 days of study medication. This is a paradoxical finding in a study that assess a drug that is administered in just 2 doses (at 1 and 8 days). However, the exclusion of patients from the CE population was done on a blinded basis, while it was not known whether patients were receiving dalbavancin+placebo or linezolid+placebo. The sensitivity analysis excluding indeterminate responses shows non-inferiority of dalbavancin as compared to linezolid.

In addition, it is potentially problematic that most point estimates for the treatment difference are on the negative side. There is a concern that the presence at TOC of significant amounts of dalbavancin in the body could biased the results, i.e. that there might in fact be a small difference in effect between both groups of treatment. Moreover, as stated above, the importance of a regular late follow up visit is related to the need to investigate whether dalbavancin could act as suppressive therapy, whether there would be a risk of regrowth after the end of exposure. It should also be noted that according to the information given by the applicant the serum levels of free dalbavancin at LFU is approximately 0.5 mg/L. Thus, patients could be considered as still under treatment even at this time point. The extraordinary pharmacokinetic properties of dalbavancin impose special requirements to the design of the clinical studies, but this issue has not been dealt with by the applicant.

The microbiologic response at the subject level for the ME at TOC population was as follows: Eradication rate was 89.5% (248/277) for dalbavancin vs. 87.5% (133/152) for linezolid. The 95% CI of the difference between eradication rates was -4.85, 8.92.

For the subset of patients with *S aureus* isolated at baseline, microbiologic response at the pathogen level for the ME at TOC population was as follows: eradication rate was 88.4% (221/250) for dalbavancin vs. 88.7% (125/141) for linezolid. Eradication rate for MRSA was 91.1% (133/146) for dalbavancin vs. 89% (65/141) for linezolid. Eradication rate for *S pyogenes* was 84.6% (11/13) for dalbavancin vs. 100% (8/8) for linezolid.

In the light of the low number of Streptococci isolates in study VER001-9, especially *S. pyogenes*, the CHMP requested the Applicant to discuss the general indication "complicated skin and soft tissue infections". The main argument of the Applicant refers to the apparent changing epidemiology of the disease with community-acquired methicillin resistant S. *aureus* (CA-MRSA) being increasingly isolated. Although outbreaks have been described in some European countries and this cannot be disregarded, this seems to be less of a problem for Europe than for the United States. It is agreed that current recommendations for the management of skin and soft tissue infections would need to be revised in the light of the increased incidence of this isolate but for the time being and in Europe, the CHMP still consider beta-haemolytic streptococci group A (GAS) to be important pathogens in SSTIs. cSSTI is a broad indication, for which coverage against GAS is considered necessary. To support this opinion reference is made to two newly published articles in which GAS is described as being an important pathogen in SSTIs (Gabillot-Carré M et all. 2007; Brook I. 2007). As stated previously the microbiological work done for dalbavancin against *S. pyogenes* seems scarce but a claim of efficacy in the SPC is not longer made. In addition, the Rapporteurs agreed with EUCAST in setting up the same breakpoints for both staphylococci and streptococci. As a consequence, this issue is considered solved.

The Applicant also clarifed that of the 492 *S. aureus* isolates in the study, 278 (56.5%) were MRSA. Based on the presence of both PVL and the SCCmec type IV genes, 64% of all of the MRSA isolates were community-acquired. In the Applicant's view these data suggest that approximately 65-70% of MRSA isolates in study VER001-9 represent MRSA sequence type USA300, the community-acquired type that has been epidemiologically linked to recurrent and often severe primary skin infections and necrotising pneumonia. Rather than being reassuring this information could be considered as problematic, i.e. that the clinical efficacy is to a large degree based on a single clonal outbreak. This would add to the concern regarding the extrapolation of the results to the general indication of Gram positive cSSTs.

As a conclusion it can be said that the lack of documented clinical efficacy against streptococci, and the fact that the clinical efficacy is to a large degree based on a single clonal outbreak of CA-MRSA in the USA underlines the need for a second confirmatory trial, as discussed below.

No clear trends were seen in subgroup analyses except for age and geographic area. Clinical success was higher among patients <65 years of age in the CE at TOC population compared with elderly patients. Dalbavancin clinical success in patients aged <65 was 90.2% (321/356) vs. 83.3% (65/78) in patients aged 65 or older. Linezolid clinical success in patients aged <65 was 91.8% (179/195) vs. 87.1% (27/31) in patients aged 65 or older. The results among patients > 75 y appears to be consistent, though the number of patients is low. Clinical success was higher in both treatment arms for patients enrolled in Europe compared with those enrolled in North America. Dalbavancin clinical success in patients enrolled in Europe was 95.3% (61/64) vs. 87.8% (325/370) in patients enrolled in North America. Linezolid clinical success in patients enrolled in Europe was 100% (38/38) vs. 89.4% (168/188) in patients enrolled in North America.

Analysis of clinical response by infection category shows that there is a trend in favour of dalbavancin in patients with cellulitis (90% vs 84%), while linezolid tends to have better outcomes in patients with major abscesses (91% vs 96%) and surgical wound infections (76.5% vs 86.4%).

Study VER001-16 (supportive)

This was a randomized, open label study in which 160 patients with complicated or uncomplicated SSTI with suspected or confirmed MRSA were randomly assigned (in a 2:1 ratio) to receive either dalbavancin or vancomycin for a total course of therapy of 14 days.

The inclusion criteria were generally similar to the inclusion criteria in Study VER001-9.Patients assigned to dalbavancin received a 1000 mg dose on Day 1 followed by a 500 mg dose on Day 8 (optional for uSSTI). Patients assigned to vancomycin received 1000 mg every 12 hours. After 24 hours of IV vancomycin, patients could switch to oral therapy. Oral therapy could be either cephalexin 500 mg four times a day for susceptible pathogens, or an oral regimen with documented in vitro activity against the patient's MRSA isolate.

The ITT population consisted of 156 patients (107 in the dalbavancin group and 49 in the vancomycin arm). The CE population at TOC included 109 patients, 79 in the dalbavancin group and 30 in the vancomycin group. The Micro ITT at TOC consisted of 76 subjects, 56 subjects in the dalbavancin group and 20 in the vancomycin group.

Types of SSSI at baseline are shown in table below.

Type of SSSI	**Dalbavancin N= 107**	**Vancomycin N= 49**
COMPLICATED	**30 (28.0)**	**18 (36.7)**
Major abscess	11 (10.3)	5 (10.2)
Cellulitis	8 (7.5)	6 (12.2)
Other deep soft tissue infection	6 (5.6)	2 (4.1)
Surgical wound infection	3 (2.8)	4 (8.2)
Traumatic wound infection	2 (1.9)	1 (2.0)
UNCOMPLICATED	**77 (72.0)**	**31 (63.3)**
Abscess not requiring Intra-operative surgical drainage	32 (29.9)	17 (34.7)
Cellulitis	23 (21.5)	4 (8.2)
Infected wounds		4 (8.2)
Infected surgical site	6 (5.6)	3 (6.1)
Infected furuncles	4 (3.7)	2 (4.1)
Other superficial skin infection	4 (3.7)	0
Impetiginous lesions	0	1 (2.0)

Regarding medical history, more patients in the vancomycin group had diabetes and a history of vascular disease compared to the dalbavancin group, as follows: 36.7% (18/49) patients in the vancomycin group had diabetes vs. 17.8% (19/107) in the dalbavancin group. Approximately, 20% (10/49) of patients in the vancomycin group had vascular disease vs. 10.3% (11/107) in the dalbavancin group.

The most frequent baseline isolate was *S aureus*. The 90% (54/60) of the recovered pathogens were *S. aureus* in dalbavancin-treated patients (ME at TOC population) and 81.8% (18/22) in vancomycin-treated patients. In the dalbavancin treated patients 70% (42/60) of the recovered pathogens were MRSA vs 50% (11/22) in vancomycin-treated patients.

Clinical response at TOC in the CE population, the primary efficacy variable, is presented in the table below.

Clinical Response in the Clinically Evaluable Population at TOC

Clinical Response	Dalbavancin		Vancomycin		Treatment Difference (%)	95% CI
Overall						
Success	71/79	(89.9%)	26/30	(86.7%)	3.2	-13.0, 19.4
cSSTI						
Success	21/25	(84.0%)	10/13	(76.9%)		
uSSTI						
Success	50/54	(92.6%)	16/17	(94.1%)		

Due to the imbalance in indeterminate responses, a post-hoc sensitivity analysis was performed using the ITT population, excluding patients with indeterminate responses. In this analysis, the clinical response was similar for both treatment groups (92.0% vs. 88.9%) and as the lower limit of the 95% CI was above the prospectively defined lower limit of -20%, non-inferiority was concluded for this analysis.

Microbiological response at the pathogen level for the ME at TOC population is presented in the table below.

Baseline pathogen	Dalbavancin	Vancomycin
All species	**N=60**	**N=22**
Success	**55 (91.7%)**	**17 (77.3%)**
Presumed Eradication	55 (91.7%)	17 (77.3%)
Failure	**5 (8.3%)**	**5 (22.7%)**
Presumed Persistence	3 (5.0%)	3 (13.6%)
Presumed Recurrence	2 (3.3%)	2 (9.1%)
Staphylococcus aureus	**N= 54**	**N= 18**
Success	**50 (92.6%)**	**15 (83.3%)**
Presumed Eradication	50 (92.6%)	15 (83.3%)
Failure	**4 (7.4%)**	**3 (16.7%)**
Presumed Persistence	2 (3.7%)	2 (11.1%)
Presumed Recurrence	2 (3.7%)	1 (5.6%)
***Staphylococcus aureus* (MRSA)**	**N= 42**	**N= 11**
Success	**38 (90.5%)**	**9 (81.8%)**
Presumed Eradication	38 (90.5%)	9 (81.8%)
Failure	**4 (9.5%)**	**2 (18.2%)**
Presumed Persistence	2 (4.8%)	2 (18.2%)
Presumed Recurrence	2 (4.8%)	0

Clinical success rates were similar in both groups. Clinical non-inferiority was concluded with a lower bound of -13%. This result, though within the predefined delta, is beyond the limit normally requested at the EU level. Microbiological eradication rates were superior in the experimental group. This data were consistent for MRSA. Overall, the open label design of the study, the delta of 20% and the uncertainties regarding the inclusion/exclusion criteria make it difficult to draw proper conclusions.

Study VER001-8 (supportive)

This was a randomized, double-blind study in which 565 patients with uncomplicated SSTI were randomly assigned (in a 2:1 ratio) to receive either dalbavancin or cefazolin for a treatment duration of 7-14 days. Uncomplicated SSTI was defined as in study VER001-16.

Patients assigned to dalbavancin received a 1000 mg dose on Day 1 with an option for a second 500 mg dose of dalbavancin on Day 8. Patients assigned to cefazolin received IV cefazolin 500 mg every 8 h, with a possible switch to oral cephalexin 500 mg every 6 h after at least 24 hours of parenteral therapy.

Patients known or suspected to have SSSI caused by MRSA at the time of enrollment, those with known bacteremia at enrollment, and those with infections that required or were anticipated to require surgical intervention/debridement during the study were excluded from participation. Enrolled patients who were later discovered to have SSSI caused by MRSA or bacteremia were to be discontinued from study medication.

Clinical entities at baseline are shown in table below.

Type of infection	Dalbavancin (N=367)	Cefazolin (N=186)
Cellulitis	145 (39.5)	75 (40.3)
Abscess not requiring intraoperative surgical drainage	61 (16.6)	28 (15.1)
Infected wounds	60 (16.3)	30 (16.1)
Erysipelas	37 (10.1)	20 (10.8)
Infected furuncles	33 (9.0)	20 (10.8)
Other superficial skin infection	19 (5.2)	7 (3.8)
Infected surgical site	10 (2.7)	6 (3.2)
Impetiginous lesions	2 (0.5)	0 (0.0)

The ITT population consisted of 553 patients (367 in the dalbavancin arm and 186 in the cefazolin arm). The total number of patients deemed clinical evaluable at TOC were 413; 266 in the dalbavancin

group versus 147 in the cefazolin group. Microbiological Response was analysed for the Micro ITT-population which in total comprised 322 patients; 224 for dalbavancin and 98 for cefazolin. The number of microbiological evaluable patients at TOC was 226 patients; 151 in the dalbavancin group and 75 in the cefazolin group.

The primary efficacy parameter was the clinical response in the clinically evaluable patient population at the TOC visit. Results are shown in table below.

Clinical Response at Test of Cure (Clinical Evaluable at TOC population)

Clinical Response	Dalbavancin (N=266)		Cefazolin (N=147)		Treatment Difference (%)	95% CI
Success	237	(89.1%)	131	(89.1%)	-0.02	-6.82, 6.79
Failure	29	(10.9%)	16	(10.9%)		

According to the protocol, patients found to have SSTI involving MRSA were to be withdrawn from study medication and treated appropriately. Therefore, the percentage of patients with a successful clinical response in the ITT population was influenced in both treatment arms by the inclusion of these patients with indeterminate clinical response as failures.

By-Patient Microbiological Response for the ME at TOC population is shown in table below.

	Dalbavancin N=151	Cefazolin N=75
Success	138 (91.4%)	65 (86.7%)
Eradication	15 (9.9%)	6 (8.0%)
Presumed Eradication	123 (81.5%)	59 (78.7%)
Failure	13 (8.6%)	10 (13.3%)
Persistence	1 (0.7%)	0 (0.0%)
Presumed Persistence	8 (5.3%)	6 (8.0%)
Recurrence	0 (0.0%)	3 (4.0%)
Presumed Recurrence	4 (2.6%)	1 (1.3%)

Microbiological response at the pathogen level for the ME at TOC population is shown in table below.

Baseline pathogen	**Dalbavancin**	**Cefazolin**
Staphylococcus aureus	**N=121**	**N=63**
Success	**110 (90.9%)**	**57 (90.5%)**
Eradication	12 (9.9%)	7 (11.1%)
Presumed Eradication	98 (81.0%)	50 (79.4%)
Failure	**11 (9.1%)**	**6 (9.5%)**
Persistente	1 (0.8%)	0 (0.0%)
Presumed Persistence	6 (5.0%)	4 (6.3%)
Recurrente	0 (0.0%)	2 (3.2%)
Presumed Recurrence	4 (3.3%)	0 (0.0%)
Streptococcus pyogenes	**N=27**	**N=9**
Success	**26 (96.3%)**	**6 (66.7%)**
Eradication	2 (7.4%)	0 (0.0%)
Presumed Eradication	24 (88.9%)	6 (66.7%)
Failure	**1 (3.7%)**	**3 (33.3%)**
Presumed Persistence	1 (3.7%)	2 (22.2%)
Recurrence	0 (0.0%)	1 (11.1%)
Streptococcus agalactiae	**N=9**	**N=5**
Success	**8 (88.9%)**	**5 (100.0%)**
Eradication	1 (11.1%)	0 (0.0%)
Presumed Eradication	7 (77.8%)	5 (100.0%)
Failure	**1 (11.1%)**	**0 (0.0%)**
Presumed Persistence	1 (11.1%)	0 (0.0%)
***Streptococcus* Group G**	**N=6**	**N=3**
Success	**4 (66.7%)**	**2 (66.7%)**
Eradication	2 (33.3%)	0 (0.0%)
Presumed Eradication	2 (33.3%)	2 (66.7%)
Failure	**2 (33.3%)**	**1 (33.3%)**
Presumed Persistence	2 (33.3%)	0 (0.0%)
Presumed Recurrence	0 (0.0%)	1 (33.3%)

There were no MRSA baseline pathogens included.

The results from the study show therapeutic non-inferiority of dalbavancin compared to cefazolin. The target population and the results of the study are of limited value to support the claimed indication.

Study VER001-4 (supportive)

This was a phase 2, randomized, open label study in which 75 patients with catheter-related blood stream infections were randomly assigned to receive weekly vancomycin, daily dalbavancin or vancomycin for up to 14 days. Daily dalbavancin was eliminated in protocol amendment 2.

Patients assigned to weekly dalbavancin received a 1000 mg dose on Day 1 followed by 500 mg on Day 8. Patients assigned to vancomycin received 1000 mg every 12 hours, with possible switch to

nafcillin or oxacillin 2000 mg every 4 hours or every 6 hours after pathogen identification and susceptibility testing.

Table below shows the microorganisms isolated at baseline.

	Weekly Dalbavancin N=26	Vancomycin N=28
Staphylococcus aureus	11 (42.3)	12 (42.9)
MRSA	5 (19.2)	9 (32.1)
CoNS	13 (50.0)	13 (46.4)
Staphylococcus capitis	1 (3.9)	0 (0.0)
Staphylococcus epidermidis	10 (38.5)	9 (32.1)
Staphylococcus haemolyticus	0 (0.0)	2 (7.1)
Staphylococcus hominis	2 (7.7)	1 (3.6)
CONS (unspeciated)	0 (0.0)	1 (3.6)
Enterococcus faecalis	2 (7.7)	3 (10.7)

The overall response in the Microbiological ITT population at TOC is shown in table below.

Table 19: Overall Response (Microbiological ITT Population at TOC)

	Weekly DAL (N=23) n (%) (95% CI)	Vancomycin (N=28) n (%) (95% CI)
Success	20(87.0) (73.2, 100.0)	14(50.0) (31.5, 68.5)
Failure	3(13.0) (0.0, 26.8)	14(50.0) (31.5, 68.5)
Failure	2(8.7)	12(42.9)
Indeterminate	1(4.4)	2(7.1)

By- Pathogen Microbiological Response at TOC (Micro ITT population) was as follows:
Eradication rate for *S aureus* was 81.8% (9/11) for weekly dalbavancin-treated patients vs. 83.3% (10/12) for vancomycin-treated patients. For MRSA there figures were 80% (4/5) for dalbavancin vs. 77.8% (7/9) for vancomycin. Eradication rate for CoNS was 100% (13/13) for dalbavancin vs. 69.2% (9/13) for vancomycin.

Overall, the study showed a better microbiological outcome with dalbavancin. However the limited size of the study is a major caveat.

In conclusion, the application is based on 1 pivotal trial assessing the efficacy of dalbavancin in patients with cSSSI. The comparator was linezolid. In the ITT analysis linezolid was superior to dalbavancin, though the lower limit of the 95%CI was within the predefined delta (12.5%). However, the primary efficacy analysis, clinical success in the CE population at TOC, showed non-inferiority of dalbavancin compared to linezolid. Microbiological data are also supportive of the efficacy of dalbavancin in the enrolled patient population.

The CHMP identified a number of major objections related to the criteria defining cSSTI and the lack of representativeness of the enrolled population in terms of severity of the disease and true need for i.v. therapy. The choice of the comparator was also questioned. Some relevant aspects questioning the quality of the pivotal study were also raised

The CHMP's view is that the concerns expressed in the Day 120 List of Questions still essentially remain. Accordingly, the Applicant will be further questioned on these aspects (see LoI). Some objections, as the issue of low hospitalisation and time to oral switch can be considered as reasonably explained, and others as the timing of the TOC, the lack insufficient quality of the information from LFU and the impossibility of conducting a separate analysis of cures and improvements cannot be solved since the information does not exist. This further highlights the limitations of Study VER001-9 as the only source of pivotal information for this trial.

Considering that pivotal study data are not sufficiently robust, the other clinical studies (VER001-5; VER001-8; VER001-16) cannot be considered as supportive for the demonstration of efficacy in cSSTI regarding the following criticisms, i.e. open-label investigations (VER001-5; VER001-16); delta: 20% (VER001-16) and only descriptive results (VER001-5); the high number of uncomplicated infections investigated (VER001-16; VER001-8).

Clinical safety

The applicant has provided the safety results pooled in two integrated safety database, which are as follows:

- Phase 1 integrated safety database: Four phase 1 studies in healthy patients and three phase 1 studies in special populations (hepatically impaired and renally impaired subjects)

- Phase 2/3 integrated safety database: Five studies, with one phase 2 open label study in patients with catheter-related broodstream infection, one phase 3 double blind study in patients with uncomplicated SSTI, two studies (one phase 2 open label and one phase 3 double blind) in patients with cSSTI and one phase 3 open label study in patients with either SSTI or cSSTI.

A total of 1257 subjects received IV dalbavancin in phase 1, 2 and 3 studies; a total of 1197 subject received a dose ≥1000 mg. In phase 2 and 3 studies patients were treated with the propose dosage of 1000 mg on day 1, 500 mg on day 8.

In phase 1 studies, a total of 141 subjects received at least one dose of IV dalbavancin with a mean exposure of 870 mg. In phase 2/3 integrated database, a total of 1126 subjects received at least one dose of dalbavancin with 707 out of the 1126 patients receiving the two doses in 14 days as the recommended posology. At this stage exposure to dalbavancin in adults in the proposed dose is considered somewhat limited, therefore the need for a second pivotal study should be considered (also in the light of the deficiencies found in study VER 001-9, see Clinical efficacy).

Final safety considerations in this report have been carried taking into account principally the results in patients receiving two doses of dalbavancin, as this is the recommended posology.

Adverse events

In the integrated phase 1 database, the most commonly reported AEs were pyrexia, reported by 21 (14.9%) subjects who received dalbavancin and headache, reported by 18 (12.8%) subjects. Other commonly reported AEs (frequency >5%) among subjects who received dalbavancin were upper respiratory tract infection (9.2%), back pain (6.4%), nausea (6.4%), and pharyngolaryngeal pain (6.4%). The frequency of each of these events was higher in subjects who received dalbavancin than in those who received placebo.

Diarrhea and fatigue were reported with greater frequency in the highest dose group of dalbavancin compared with the lower dalbavancin dose groups:

- Diarrhea was reported by 5 (14.7%) subjects who received >1000 mg dalbavancin, 1 (1.3%) subject who received 630 mg dalbavancin, 1 (3.4%) subject who received 140 mg dalbavancin, and 1 (5.3%) subject who received placebo. All AEs of diarrhea were mild or moderate in intensity and resolved completely.

- Fatigue was reported by 5 (14.7%) subjects who received >1000 mg dalbavancin, 1 (1.3%) subject who received 1000 mg dalbavancin, and 1 (5.3%) subject who received placebo. All AEs of fatigue were mild in intensity and resolved completely.

For the Phase 2/3 integrated safety database, comparators are heterogeneous (vancomycin, linezolid, cefazolin) with possible switch to oral therapy, which makes it difficult to draw appropriate conclusions.

An overview of adverse events occurring in > 2% of patients in any dosing subgroup is provided in table below.

Table 1. Adverse Events Occurring in >2% of Patients in Any Dosing Subgroup: Phase 2/3 Integrated Database [Number (%) of Patients]

Preferred Term	Dalbavancin n (%)			Comparator n (%)		
	1 Dose (N = 419)	2 Doses (N = 707)	Total (N = 1126)	7 Days (N = 176)	14 Days (N = 397)	Total (N = 573)
Patients with at least 1 AE	**169 (40.3)**	**416 (58.8)**	**585 (52.0)**	**73 (41.5)**	**253 (63.7)**	**326 (56.9)**
Nausea	19 (4.5)	50 (7.1)	**69 (6.1)**	12 (6.8)	35 (8.8)	**47 (8.2)**
Diarrhea NOS	24 (5.7)	39 (5.5)	**63 (5.6)**	8 (4.5)	31 (7.8)	**39 (6.8)**
Headache	13 (3.1)	41 (5.8)	**54 (4.8)**	5 (2.8)	28 (7.1)	**33 (5.8)**
Constipation	6 (1.4)	34 (4.8)	**40 (3.6)**	2 (1.1)	17 (4.3)	**19 (3.3)**
Vomiting NOS	10 (2.4)	30 (4.2)	**40 (3.6)**	6 (3.4)	20 (5.0)	**26 (4.5)**
Urinary tract infection NOS	5 (1.2)	29 (4.1)	**34 (3.0)**	1 (0.6)	11 (2.8)	**12 (2.1)**
Anemia NOS	8 (1.9)	23 (3.3)	**31 (2.8)**	2 (1.1)	10 (2.5)	**12 (2.1)**
Rash NOS	9 (2.1)	20 (2.8)	**29 (2.6)**	4 (2.3)	9 (2.3)	**13 (2.3)**
Pruritus	9 (2.1)	16 (2.3)	**25 (2.2)**	4 (2.3)	10 (2.5)	**14 (2.4)**
Insomnia	4 (1.0)	19 (2.7)	**23 (2.0)**	4 (2.3)	22 (5.5)	**26 (4.5)**
Hyperglycemia NOS	3 (0.7)	18 (2.5)	**21 (1.9)**	1 (0.6)	11 (2.8)	**12 (2.1)**
Abdominal pain NOS	3 (0.7)	17 (2.4)	**20 (1.8)**	4 (2.3)	5 (1.3)	**9 (1.6)**
Blood lactate dehydrogenase increased	6 (1.4)	14 (2.0)	**20 (1.8)**	0	12 (3.0)	**12 (2.1)**
Dyspepsia	4 (1.0)	16 (2.3)	**20 (1.8)**	2 (1.1)	4 (1.0)	**6 (1.0)**
Gamma-glutamyl-transferase increased	4 (1.0)	16 (2.3)	**20 (1.8)**	1 (0.6)	12 (3.0)	**13 (2.3)**
Hypoglycemia NOS	2 (0.5)	15 (2.1)	**17 (1.5)**	2 (1.1)	9 (2.3)	**11 (1.9)**
Pyrexia	4 (1.0)	13 (1.8)	**17 (1.5)**	2 (1.1)	11 (2.8)	**13 (2.3)**
Fatigue	5 (1.2)	8 (1.1)	**13 (1.2)**	4 (2.3)	9 (2.3)	**13 (2.3)**
ALT increased	2 (0.5)	9 (1.3)	**11 (1.0)**	3 (1.7)	9 (2.3)	**12 (2.1)**
AST increased	2 (0.5)	4 (0.6)	**6 (0.5)**	4 (2.3)	3 (0.8)	**7 (1.2)**
Loose stools	1 (0.2)	5 (0.7)	**6 (0.5)**	1 (0.6)	13 (3.3)	**14 (2.4)**

Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days was based on actual exposure, not randomized treatment. Patients are counted only once at each level of summarization. AEs are presented in decreasing frequency of preferred term for the total dalbavancin arm.
Source: Appendix 2.7.4A, Table 4.8-2.1. Includes data from Studies VER001-4, VER001-5, VER001-8, VER001-9, and VER001-16.

A total of 585 (52.0%) of dalbavancin treated patients and 326 (56.9%) of comparator treated patients reported at least one adverse event. Apparently there were no important differences between the treatment groups in the adverse events profile. However, there is a slight tendency for the AEs reported in the dalbavancin group to be categorised as severe more often than in the comparator group, especially for the «2 doses»-group. Gastrointestinal disorders were the most commonly reported adverse events in the phase 2/3 database, observed in 19.3% of dalbavancin treated patients and 23.0% of patients in the comparator group.

There are some concerns regarding methodology in the reporting of adverse events. The applicant states that all AEs through the follow-up visit were included in the safety analysis. However, the Last Follow Up was a telephone call and not a regular visit, and in addition, was not performed for all patients in the clinical studies. Furthermore, patients were during this interview only asked for any

SAEs (i.e., visits to emergency departments and / or hospital admissions since the TOC visit). The applicant was asked to discuss to whether relevant safety information might have been lost, also taken into consideration the significant amount of dalbavancin still present at TOC. In addition, some of the reported AEs seem not to have been followed until resolution, i.e. were still ongoing at end of study with unknown outcome.

In the applicant responses, new information has been provided showing that at least some AEs were reported beyond the TOC visit. Thus the safety database does contribute some knowledge about the safety profile also after the 14 days treatment period.

Treatment-related adverse events

Treatment-related AEs are those events that were considered by the investigator, and/or the Sponsor, as possibly or probably related to study treatment. A summary of treatment-related AEs occurring in >2.0% of treated subjects (overall) has been presented for both integrated safety analysis.

In the integrated safety analysis for phase 1 studies, treatment related AE were reported by 50 (35.5%) patients in phase 1 studies. The most commonly reported treatment-related AE was pyrexia and headache, which were reported by 14 (9.9%) and 6 (4.3%) of subjects who received dalbavancin. Treatment-related 'deafness', which was reported in 5 (3.5%) subjects who received dalbavancin and 2 (10.5%) subjects who received placebo, all occurred in Study VER001-1. A review of the blinded data by expert audiologists was conducted. The review concluded that the changes observed were at random and probably attributable to poor data collection techniques. Consequently, the audiologic criteria were modified for the assessment performed in the following studies.

For the Phase 2/3 integrated safety database, a greater percent of both dalbavancin and comparator treated patients who received 2 doses or 14 days of treatment had treatment-related AEs compared with those who received 1 dose or 7 days of treatment. Treatment-related adverse events were reported by 248 (22%) subjects treated with dalbavancin and 157 (27.4%) subjects who received comparator. Gastrointestinal disorders were the most commonly reported type of treatment-related AE, as 89 (7.9%) dalbavancin-treated patient patients had at least 1 event in this system organ class

In dalbavancin-treated patients overall, the common treatment-related AEs were as follows: diarrhea (3.0%), nausea (2.8%), increased gamma-glutamyl-transferase (1.4%), rash (1.4%), vomiting (1.2%), increased blood lactate dehydrogenase (1.2%), and headache (1.2%). All other treatment-related AEs were categorized as 'uncommon', i.e., occurring at a frequency of ≥0.1% to <1%. An overview of these treatment-related adverse events is provided in table below:

Table 4.7-2.1
(Page 1 of 2)
Treatment-Related Adverse Events Reported in >1% of the Patients in any Treatment Arm
Phase 2/3 Overall
ITT Population

AE Preferred Term	Dalbavancin 1 dose (N=419)	Dalbavancin 2 doses (N=707)	Total Dalbavancin (N=1126)	Comparator 7 days (N=176)	Comparator 14 days (N=397)	Total Comparator (N=573)
Number (%) of patients with at least one treatment-related AE	62 (14.8)	186 (26.3)	248 (22.0)	33 (18.8)	124 (31.2)	157 (27.4)
DIARRHOEA NOS	14 (3.3)	20 (2.8)	34 (3.0)	3 (1.7)	18 (4.5)	21 (3.7)
NAUSEA	9 (2.1)	23 (3.3)	32 (2.8)	6 (3.4)	14 (3.5)	20 (3.5)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	4 (1.0)	12 (1.7)	16 (1.4)	1 (0.6)	7 (1.8)	8 (1.4)
RASH NOS	7 (1.7)	9 (1.3)	16 (1.4)	2 (1.1)	4 (1.0)	6 (1.0)
VOMITING NOS	4 (1.0)	10 (1.4)	14 (1.2)	2 (1.1)	4 (1.0)	6 (1.0)
HEADACHE	0	13 (1.8)	13 (1.2)	2 (1.1)	6 (1.5)	8 (1.4)
BLOOD LACTATE DEHYDROGENASE INCREASED	3 (0.7)	10 (1.4)	13 (1.2)	0	7 (1.8)	7 (1.2)
ALANINE AMINOTRANSFERASE INCREASED	2 (0.5)	7 (1.0)	9 (0.8)	3 (1.7)	6 (1.5)	9 (1.6)
LIVER FUNCTION TEST ABNORMAL	0	9 (1.3)	9 (0.8)	0	4 (1.0)	4 (0.7)
PRURITUS	2 (0.5)	5 (0.7)	7 (0.6)	1 (0.6)	6 (1.5)	7 (1.2)
VAGINOSIS FUNGAL NOS	1 (0.2)	6 (0.8)	7 (0.6)	2 (1.1)	5 (1.3)	7 (1.2)
BLOOD URIC ACID INCREASED	0	7 (1.0)	7 (0.6)	0	4 (1.0)	4 (0.7)
ASPARTATE AMINOTRANSFERASE INCREASED	2 (0.5)	3 (0.4)	5 (0.4)	4 (2.3)	2 (0.5)	6 (1.0)

LOOSE STOOLS	0	4 (0.6)	4 (0.4)	0	8 (2.0)	8 (1.4)
ORAL CANDIDIASIS	0	3 (0.4)	3 (0.3)	1 (0.6)	6 (1.5)	7 (1.2)
URTICARIA NOS	2 (0.5)	0	2 (0.2)	2 (1.1)	1 (0.3)	3 (0.5)
THROMBOCYTOPENIA	0	1 (0.1)	1 (0.1)	1 (0.6)	7 (1.8)	8 (1.4)
FLUSHING	0	1 (0.1)	1 (0.1)	1 (0.6)	5 (1.3)	6 (1.0)

Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days is based on true exposure, not randomized treatment. Treatment-related AEs are defined as those reported as possibly or probably related to study treatment or AEs for which the relationship was missing. Patients are only counted once at each level of summarization. Adverse events are presented in decreasing frequency of preferred term for the total dalbavancin arm.
Source: Integrated CTD database: Phase 2/3 studies (VER001-4, VER001-5, VER001-8, VER001-9, VER001-16).

Serious Adverse Events and deaths

In relation to the number of deaths in clinical trials, no subject died during the Phase 1 clinical studies. Nine (0.8%) dalbavancin-treated patients and 7 (1.2%) comparator-treated patients died during phase 2/3 studies. All adverse events resulting in death were considered as unrelated to study or unlikely related to study drug, however the case report of one dalbavancin patient who developed spontaneous bleeding of the tracheostomy seems intriguing. The applicant was asked to discuss this in relation to any other possible data on influence of dalbavancin on platelet activity.

The applicant states that the case above mentioned was complicated by numerous comorbidities and concurrent medications, including the use of heparin for DVT prophylaxis during the 3 days just before the episode of bleeding. It is agreed that the patients had several other risk factors which could be the cause of the event.
The numbers reported with regard to AEs related to platelet activity or bleeding time are too low to reveal any possible trend.

As requested, the applicant furthermore reviewed both clinical and non-clinical data to investigate whether there is any evidence to suggest that dalbavancin may influence platelet activity or blood coagulation. The applicant concludes that there is no evidence of an adverse effect of dalbavancin on platelet activity, or blood coagulation throughout the non-clinical studies. The applicant also states that, taken together all clinical database, the available data support the lack of a significant effect of dalbavancin on platelet counts, coagulation tests, and bleeding-related adverse events.

Regarding the non-clinical data, the CHMP is of a somewhat different opinion than the applicant. In our opinion, the non-clinical data cannot exclude an effect of bleeding time; however there are no clear signals in the clinical data. As the events are adequately covered in point 4.8 of the SPC, we considered the issue solved.

In the Phase 2/3 database 92 (8.2%) dalbavancin-treated patients and 54 (9.4%) comparator-treated patients experienced at least 1 SAE, see table below. There seems to be a slightly higher incidence of infection related SAEs in the dalbavancin group. This is more pronounced in the cSSTI population, exemplified with cellulitis reported by 10 (1.6%) in the dalbavancin group and 1 (0.3%) in the comparator group. There is a concern that might possibly be a reflection of a higher frequency of treatment failure in the dalbavancin group.

In the responses, the applicant shows that the frequency of Infection and infestation SAEs, for the Phase 2/3 ITT population, was slightly lower for dalbavancin than comparator treatments (36/1126, 3.2% versus 22/573, 3.8% respectively). The frequency of SAEs for the same system organ class, restricted to just the cSSTI population, is comparable between dalbavancin (24/642, 3.7%) and the comparator treatment arms (12/322, 3.7%).

The applicant acknowledges that cellulites was reported at a higher frequency for dalbavancin treated patients (10/642, 1.6%) than comparator (1/322, 0.3%) in the Phase 2/3 cSSTI ITT patient population. These 10 patients have been discussed in more detail. All SAEs classified as cellulitis seems to be treatment failures and should have been classified as such; this includes 7 patients in the pivotal study VER001-9. Of these 7 patients, two were apparently classified as clinical success at TOC and both seem to have experienced new or worsening of infection in the follow up period. With regard to the other concern, the two cases of cellulites in the pivotal study classified as clinical success do not influence the results to such degree that any reanalysis is needed. However, in the CHMP's opinion

this to some degree strengthens the concerns expressed in Major Objection 145, regarding the lack of a regular Late Follow Up visit for assessment of clinical cure.

Table 7: Serious Adverse Events Occurring in 2 or More Dalbavancin-Treated Patients: Phase 2/3 Integrated Database [Number (%) of Patients]

Preferred Term	Dalbavancin n (%)			Comparator n (%)		
	1 Dose (N = 419)	2 Doses (N = 707)	Total (N = 1126)	7 Days (N = 176)	14 Days (N = 397)	Total (N = 573)
Patients with at least one SAE	**33 (7.9)**	**59 (8.3)**	**92 (8.2)**	**19 (10.8)**	**35 (8.8)**	**54 (9.4)**
Cellulitis	6 (1.4)	7 (1.0)	**13 (1.2)**	3 (1.7)	2 (0.5)	**5 (0.9)**
Abscess limb	1 (0.2)	2 (0.3)	**3 (0.3)**	0	0	**0**
Cardiac failure congestive	1 (0.2)	2 (0.3)	**3 (0.3)**	1 (0.6)	0	**1 (0.2)**
Infection NOS	2 (0.5)	1 (0.1)	**3 (0.3)**	0	1 (0.3)	**1 (0.2)**
Osteomyelitis NOS	0	3 (0.4)	**3 (0.3)**	1 (0.6)	2 (0.5)	**3 (0.5)**
Accidental overdose	1 (0.2)	1 (0.1)	**2 (0.2)**	0	1 (0.3)	**1 (0.2)**
Asthma NOS	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Atrial fibrillation	1 (0.2)	1 (0.1)	**2 (0.2)**	0	1 (0.3)	**1 (0.2)**
Cardio-respiratory arrest	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Cardiopulmonary failure	2 (0.5)	0	**2 (0.2)**	0	0	**0**
Deep vein thrombosis	0	2 (0.3)	**2 (0.2)**	0	1 (0.3)	**1 (0.2)**
Febrile neutropenia	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Impaired healing	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Leukopenia NOS	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Myocardial infarction	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Perianal abscess	0	2 (0.3)	**2 (0.2)**	0	1 (0.3)	**1 (0.2)**
Peripheral ischemia	1 (0.2)	1 (0.1)	**2 (0.2)**	0	0	**0**
Pneumonia NOS	1 (0.2)	1 (0.1)	**2 (0.2)**	1 (0.6)	1 (0.3)	**2 (0.3)**
Pyrexia	1 (0.2)	1 (0.1)	**2 (0.2)**	0	1 (0.3)	**1 (0.2)**
Respiratory failure	0	2 (0.3)	**2 (0.2)**	0	0	**0**
Skin and subcutaneous tissue abscess NOS	2 (0.5)	0	**2 (0.2)**	0	0	**0**

Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days was based on actual exposure, not randomised treatment. Patients are counted only once at each level of summarization. AEs are presented in decreasing frequency of preferred term for the total dalbavancin arm.
Includes data from Studies VER001-4, VER001-5, VER001-8, VER001-9, and VER001-16.

Two patients (0.2%) treated with dalbavancin and 5 (0.9%) treated with a comparator drug, had a total of 7 SAEs that were considered to be related to treatment. The two SAEs reported for dalbavancin-treated subjects was leucopenia NOS.

Discontinuations due to adverse events

Regarding discontinuations, in phase 1 studies, there were 3 subjects who had AEs that led to discontinuation of study drug. One patient had a mild allergic reaction during infusion of a single 840 mg single dose of dalbavancin. The event was considered probably related to study drug. Other subject did not receive the second dose (had received the first 1000 mg dose) due to a severe constipation, which was considered possibly related to study drug. The third patient had a mild allergic reaction possibly related to dalbavancin after received a single 1000 mg dose that resulted in premature discontinuation.

For phase 2/3 studies, the percentage of patients who had at least 1 AE that resulted in discontinuation of study drug was 3.5% (39 patients). AEs resulting in discontinuation of study medication for 2 or more patients in any treatment arm are summarized by AE preferred term in Table 2.

Table 2. All-Causality Adverse Events Resulting in Discontinuation of Study Drug for 2 or More Patients in Any Treatment Arm: Phase 2/3 Integrated Database [Number (%) of Patients]

Preferred Term	Dalbavancin n (%)			Comparator n (%)		
	1 Dose (N = 419)	2 Doses (N = 707)	Total (N = 1126)	7 Days (N = 176)	14 Days (N = 397)	Total (N = 573)
Patients with at least 1 AE leading to discontinuation	**33 (7.9)**	**6 (0.8)**	**39 (3.5)**	**13 (7.4)**	**9 (2.3)**	**22 (3.8)**
Rash	3 (0.7)	2 (0.3)	**5 (0.4)**	1 (0.6)	1 (0.3)	**2 (0.3)**
Osteomyelitis NOS	4 (1.0)	0	**4 (0.4)**	0	0	**0**
Cellulitis	3 (0.7)	0	**3 (0.3)**	1 (0.6)	0	**1 (0.2)**
Diarrhea NOS	2 (0.5)	0	**2 (0.2)**	1 (0.6)	0	**1 (0.2)**
Infection NOS	2 (0.5)	0	**2 (0.2)**	0	0	**0**
Insomnia	1 (0.2)	1 (0.1)	**2 (0.2)**	0	0	**0**
Pruritus	2 (0.5)	0	**2 (0.2)**	0	0	**0**
Rash generalized	2 (0.5)	0	**2 (0.2)**	0	0	**0**
Skin and subcutaneous tissue abscess NOS	2 (0.5)	0	**2 (0.2)**	0	0	**0**
Nausea	1 (0.2)	0	**1 (0.1)**	4 (2.3)	0	**4 (0.7)**
Pneumonia NOS	0	1 (0.1)	**1 (0.1)**	2 (1.1)	0	**2 (0.3)**
Urticaria NOS	1 (0.2)	0	**1 (0.1)**	1 (0.6)	1 (0.3)	**2 (0.3)**
Renal failure acute	0	0	**0**	1 (0.6)	1 (0.3)	**2 (0.3)**
Vomiting NOS	0	0	**0**	2 (1.1)	0	**2 (0.3)**

Note: Patient assignment to 1 dose or 7 days versus 2 doses or 14 days was based on actual exposure, not randomized treatment. Patients are counted only once at each level of summarization. AEs are presented in decreasing frequency of preferred term for the total dalbavancin arm.
Source: Appendix 2.7.4A, Tables 4.5.1-2 and 4.5-3. Includes data from Studies VER001-4, VER001-5, VER001-8, VER001-9, and VER001-16.

Fourteen (1.2%) dalbavancin-treated patients and 12 (2.1%) comparator-treated patients had a treatment-related AE that resulted in discontinuation of study medication. Treatment-related AEs resulting in discontinuation of study medication in dalbavancin-treated patients include rash NOS (0.4%), pruritus (0.2%), generalized rash (0.2%), urticaria NOS (0.1%) and nausea (0.1%).

Nephrotoxicity and use in patients with renal impairment

Nephrotoxicity is considered as a class effect of glycopeptides, and the kidneys were target organs for dalbavancin toxicity in the non-clinical studies. In the clinical safety database, however, such effects do not seem to be very apparent, and there seems to be no clear differences between the treatment groups. Renal disorder adverse events were reported by 2.6% of dalbavancin treated patients compared to 3.1% who received comparator. One of the renal disorder (renal failure) was considered to be probably related to the study drug.

However, patients with creatinine clearance < 50 ml/min were excluded from the clinical studies, and the integrated Phase 2/3 database includes only 24 (2.1%) dalbavancin-treated patients and 22 (3.8%) comparator treated patients in this category of renal function. The cSSTI studies only contribute with approximately half of these patients. It has been discussed for other glycopeptides that patients with reduced renal function might be at a higher risk of renal adverse events than patients with normal renal function. Therefore, there is a need to investigate whether the nephrotoxic potential of dalbavancin could be greater in this patient group than what is indicated in the submitted clinical data. In addition, it is not stated whether the phase 1 subject who experienced ESRD received dalbavancin or placebo, this should be clarified by the applicant.

Furthermore, due to the small sample size for this patient group, a meaningful comparison of adverse event profile by baseline renal impairment is not possible. In summary, there is not enough data to justify the extrapolation of safety data to patients with moderate-severe renal impairment.

Applicant response to the issue mentioned above, focuses on patients in the two phase 3 studies (VER001-8 and VER001-9). The applicant's response confirms that there is a very limited number of patients with CrCL < 50 ml/min included. Although the results of the pharmacokinetic modelling provide information about the exposure of dalbavancin in these patients with the proposed dosage, there is not sufficient data to provide reassurance with regard to safety, especially renal safety.

In conclusion, neprhotoxicity is a class effect for glycopetide antibiotics. Admittedly, dalbavancin does not appear to be particularly more nephortoxic than available glycopeptides. The CHMP however considers that this aspect would deserve further evaluation and the Applicant should present a proposal on how this aspect is intended to be further studied. Meanwhile, the dosing recommendation based on PK simulations proposed in the SPC could be deemed acceptable, though a clear warning highlighting the limitation of the clnical database should be included.

Liver toxicity

Also the liver was a target organ for toxicity in the non-clinical studies. Although hepatic changes were severe and partly irreversible in the non-clinical studies and the safety margins were narrow or unidentifiable, hepatotoxicity was not a specific matter of concern in the clinical safety database.

Results from a Phase I study indicate a possible lower exposure of dalbavancin in patients with severe liver impairment. In the clinical studies the incidence of hepatic AEs and hepatobiliary abnormalities was low with no apparent difference to the comparator group.

The conclusion in the safety summary is, however, in contrast with the measures proposed by the applicant regarding this adverse event, as reflected in the RMP and section 4.4 of the SPC. Overall, there seem to be evidence to support the concerns about the size of the safety database. As a consequence, the applicant should discuss whether monitoring of patients could be necessary, also taking into account that the hepatotoxic risk may increase if patients would be treated for longer periods or repeatedly. Furthermore, as patients are exposed to dalbavancin for a rather long period of time after cessation of treatment, the Applicant should discuss how to manage liver toxicity clinically.

Although size of the pre-approval database is limited, data suggest a low incidence of hepatic AEs and hepatobiliary abnormalities. The applicant states that the SPC wording was added as a cautionary approach. However, specific wording regarding the monitoring of hepatic events will not be included in the SPC. Dalbavancin will be monitored by routine pharmacovigilance, which will include regular review of hepatobilary adverse events as Targeted Medical Events. This will included analysis of events in off-label longer term use.

Currently measures proposed are considered sufficient (SPC and RMP ammendements). Routine monitoring of patients is not deemed necessary.

Audiology

Audiometry was performed in 6 phase I studies, but not in patients included in the phase III trials. Although study VER001-12 was performed in patients with normal and impaired hepatic function treated with the dosage applied for, most subjects included in these studies were healthy volunteers administered different dosages. Study VER001-13 included patients with mild-moderate renal impairment who received single doses of 1000 mg dalbavancin. In phase 2/3 studies, there were 3 treatment-related adverse events reported for dalbavancin and none in comparators. Two (0,3%) cases of tinnitus in patients treated with two doses and 1 (0.2%) case of vertigo in a patient treated with one dose. According to the applicant, the review of the totality of the data, the results do not suggest any

pattern of **ototoxic** change associated with dalbavancin. The applicant was requested to discuss if the submitted data was sufficient to exclude ototoxicity in patients treated with the proposed dosing schedule, and particularly patients with reduced renal function.

The applicant presents a review of the audiology results for VER001-3, VER001-10, VER001-12 and VER001-13 and review of the additional adverse event data from studies VER001-9, VER001-8 and VER001-16. Complete audiologic testing was performed in VER001-2 (dalbavancin n = 39), VER001-3 (dalbavancin n = 5), VER001-10 (dalbavancin n = 6), VER001-12 (dalbavancin n = 21 of 27), and VER001-13 (dalbavancin n = 16 of 21) including patients with mild or renal impairment. Forty-three subjects who had complete audiologic evaluations received clinically relevant doses of dalbavancin, 1000 mg x 1 or 1000 mg followed by 500 mg on Day 8. Applicant's position is that the results can be attributed to subject variability. The review of the totality of the data submitted does not suggest any pattern of ototoxic change associated with dalbavancin. However, we still have concerns about patients with reduced renal function. Audiometry was performed in 6 phase I studies but not in phase 3 studies and with different dosages. Of the three phase 1 studies including patients with renal impairment, only in study VER 000-12 patients received the proposed dosing schedule. At present, we still think that there is not sufficient data to exclude a possible ototoxic effect, especially in patients with renal impairment.

Glucose homeostasis

In the Phase 2/3 safety population, AEs potentially related to glucose homeostasis were reported with similar frequencies in the two treatment groups. A total of 49 (4.4%) dalbavancin treated patients and 29 (5.1%) in the comparator group reported at least one such event. However, with regard to serum chemistry, hyperglycemia was observed in 7 (0.7%) of dalbavancin treated patients and 1 (0.2%) of comparator treated. Hypoglyceamia was reported in 5 (0.5%) of dalbavancin treated and none comparator treated patients. Serious adverse events relating to glucose homeostasis were reported in 1 (0.1%) dalbavancin-treated patient (diabetes mellitus inadequate control) and 1 (0.2%) comparator treated patient (hypoglycaemia NOS). Neither event was considered to be related to treatment.

As diabetic patients constitute an important group of potential users of dalbavancin, the applicant should thoroughly discuss possible consequences for control of blood glucose in diabetic patients. In addition, a discussion on blood glucose concentrations before and during dalbavancin treatment was requested, including a description of concomitant medications related with glycaemic control.

The applicant underlines that the interpretation of blood glucose values in diabetic patients in the dalbavancin clinical programme is problematic for the following reasons:

- Lack of historical blood glucose values.
- Unknown fasting or non-fasting condition.
- Timing of blood sample with respect to antidiabetic drugs administration is not known.
- Infection often precipitates elevated blood glucose levels in diabetic patients, and may in fact be the first sign of an otherwise occult infection.

The applicant analyses glucose levels, concomitant medications and adverse events potentially related effects on glucose homeostasis and considers that, in view of the data, there is not a significant risk for dalbavancin causing clinically significant glucose dysregulation in patients, and more specifically in diabetic patients.

CHMP supports that AEs potentially related to glucose homeostasis were reported with similar frequencies by dalbavancin and comparator treated patients. The issue related to the fact that, with regard to serum chemistry, hyperglycaemia was reported for 7 subjects (0.7%) in the dalbavancin group and 1 subject (0.2%) in the comparator group. Hypoglycaemia was reported in 5 (0.5%)

dalbavancin and none comparator treated patients. The numbers are, admittedly, low and not supported by any difference in the reported AEs.

Myelosuppression

In the overall Phase 2/3 population, adverse events potentially related to myelosuppression occurred in 42 patients (3.7%) in the dalbavancin group and 26 (4.5%) in the comparator group. Neutropenia was reported in 1 (0.1%) dalbavancin treated patient and no comparator treated patients. Thrombocytopenia was reported in 2 (0.2%) dalbavancin treated patients and 8 (1.4%) comparator treated patients.

The comparator in the pivotal trial, contributing with the highest number of patients, was linezolid, known to cause myelosuppression. Although the incidence of thrombocytopenia was higher in the linezolid group in VER001-9 (7 (2.5%) vs 1 (0.2%)), the incidence of anaemia was higher in the dalbavancin group (18 (3.2%) vs 4 (1.4%)). Also in the overall Phase 2/3 database the incidence of anaemia is slightly higher in the dalbavancin group than in the comparator group. Anaemia reported by 19 (3%) patients treated with dalbavancin and 7 (2.2%) patients treated with comparators. Of these, 10 (0.9%) cases of anaemia were considered as related to dalbavancin and none in the comparator group. Thus whether the safety profile of dalbavancin with respect to myelosuppression is better than for the comparators, as stated by the applicant, is disputable.

The applicant was requested to discuss the potential risk of myelosuppression with dalbavancin, especially the risk of anaemia. Additionally, the clinical importance of the frequencies of such events in relation to the known risk of myelosuppression imposed by linezolid should also be discussed.

The applicant concludes that in Phase 2/3 clinical trials, adverse events associated with myelosuppression occurred at a lower frequency in dalbavancin- than in comparator treated patients (3.7% vs. 4.5%, respectively). For haematology parameters, few patients in either treatment groups showed potentially significant decreases in haemoglobin, white blood cells, neutrophils, or platelets. The percentages of patients with changes were similar or lower in the dalbavancin-treated patients. Low magnitude and reversible changes in haematological parameters were observed in dalbavancin preclinical studies. The incidence of adverse events related to anaemia in Phase 2/3 clinical studies was similar between dalbavancin and comparator treated arms and the incidence of adverse events related to myelosuppression occurred at a lower frequency in dalbavancin-treated patients. Shift analyses for haemoglobin values were similar for dalbavancin-treated patients and comparator-treated patients.

The haematological effects of linezolid are well documented and are usually duration or dose dependent. Literature indicates that the risk of thrombocytopaenia with teicoplanin usually at occurs at doses exceeding the recommended posology. In the CHMP's opinion, although it is accepted that duration of therapy seems to be an important factor for linezolid mediated myelosuppression, a slightly lower incidence of such events in the dalbavancin group does not necessarily allow for the conclusion that the risk is low. And there definitely seems to be a risk of anaemia connected to dalbavancin treatment. Nevertheless, the frequency of thrombocytopenia is higher in the comparator group, and the listing of these events, including anaemia, seems adequate in point 4.8 of the SPC.

Effects on the QT-interval

The Applicant justifies the absence of a dedicated QTc study according to current international requirements due to the fact that when the clinical development of the drug was initiated the current international recommendations were not in place. This strictly calendar-based justification is hardly acceptable for a dossier submitted for evaluation more than 2 years after the current guidelines came into operation. An evaluation of the QT prolongation potential was performed for patients in both the Phase 1 and the Phase 2/3 data set. There are some concerns regarding whether the ECG-recordings fulfil the criteria for assessment of potential QT prolonging effects of dalbavancin. The applicant is asked to discuss the sensitivity of ECG method used, the lack of proper positive (and negative)

controls and generally methodology used, compared to the present guidelines (ICH E14). Although the incidence of QT-prolongation was similar in the two treatment groups, the fact that 6.3% of the patients had an increased QTcB of >30-60 msec in overall phase 2/3 studies causes some difficulties in endorsing the applicant's conclusion that there is a minimal risk of QT-prolongation. The need for a dedicated QT study according to ICH E14 guideline should be addressed in the light of the previous comments.
Finally, what is not justify, specially considering the lack of a QT specific study, is the non inclusion of this aspect in the RMP and pharmacovigilance plan, at least until more experience of use with the drug is available, thus leading to exclude the risk with a sufficient level of certainty.

To address the issues raised above, the applicant has presented a resume of clinical studies where QT interval is assessed (phase 1 studies and integrated phase 2/3). A summary of preclinical studies are also presented (HERG, APD assay, canine telemetry). In addition two appendices are presented showing the computational study on shape and size of Dalbavancin comparing HERG channel and structural comparison of Dalbavancin and Telavancin.

With regard to preclinical data, the CHMP has the following comments:

- We agree that Telemetred dog data gives no evidence for proarrhythmic potential of Dalbavancin
- HERG inhibition data is clean, however two important limitations are the concentration of the test drug used not exceeding free human Cmax and the lack of actual Dalabavancin concentration measurement in the test tube. This drug is lipophilic and may to some degree adsorb to the test system (tubing etc.), as discussed for Question 146.2 and 148.5.
- Action Potential D assay actually shows a dose dependent increase of APD at all stimulation frequencies even the increase is not statistically significant comparing to vehicle.

In relation to clinical data presented, the analysis of phase 1 data and integrated phase 2/3 data suggest that there is no increase in mean QT/QTc compared to placebo and comparators (vancomycin in phase 2 and cefazolin in phase 3), respectively. In summary: Dalbavancin does not increase mean QTc in the present clinical program above 5 msec that is the threshold of regulatory concern. One clinical study (VER001-4) although shows twice number of patients with increased QTc above 30 msec and less than 60 msec from baseline. The objective on the lack of positive control or an alternative method to establish assay sensitivity is still not discussed and weakens conclusions made in the present studies.

Overall, Dalbavancin has some unresolved preclinical issues concerning both HERG and APD assays as well. Concentration of Dalbavancin in the HERG assay is not high enough to exclude inhibitory effect on the HERG channel.

The Applicant argument that the clinical development of dalbavancin was made before the current recommendations on the conduction of a dedicated QT study were available is acknowledged but not deemed a proper justification. An effect on drug repolarisation has been described for other drugs of the same therapeutic class and the available non-clinical and clinical data for dalbavancin do not allow to firmly rule out such effect. Consequently the conduction of a thorough QT study seems unavoidable. This could be probably acceptable as a post-approval commitment, provided that the SPC includes a warning highlighting that an effect of dalbavancin on cardiac repolarisation cannot be excluded and might potentially be of clinical significance. All the precautions for drugs showing a prolonging QT effect should also be included. Once the results of the requested study are provided, the SPC could be amended accordingly.

<u>Skin associated adverse events</u>

In the Phase 2/3 database there were 13 cases (9 dalbavancin, 4 comparators) of treatment-related rash and other skin events that led to discontinuation of study medication. All but 2 were mild or moderate

in intensity. The 2 severe treatment-related rashes were each reported by patients who received 1 dose of dalbavancin.

The long half-life of dalbavancin is considered as a potential concern in relation to allergic reactions. Although such reactions do not seem to be common, and are reported with equal frequencies in comparator treated as in dalbavancin treated patients, the duration of these reactions are longer in the dalbavancin group. It is also of concern that the patient with a treatment related rash ongoing at end of study was not followed until resolution.

Overall, the Applicant should comment on the clinical handling in case of severe allergic reactions and other severe treatment-related adverse events (e.g. Stevens-Johnson Syndrome, Epidermolysis bullosa, hepatic failure, rhabdomyolysis, pseudomembraneous colitis etc.) where immediate stopping of the treatment is a pillar of the handling of such diseases.

The Applicant did not completely answer the question. At the moment the only option in case of severe allergic reactions or other severe adverse reactions is supportive care. Dalbavancin is not rapidly removed by dialysis. The applicant is currently supporting investigator research on methods to more rapidly remove dalbavancin and detailed information of this research should be provided.

Pharmacological class adverse reactions

There are class adverse reactions that have been previously reported with lipoglycopeptide antibiotics. Such reactions may include superinfection, blood and lymphatic disorders, ear and labyrinth disorders, gastrointestinal disorders, antibiotic-associated and pseudomembraneous colitis, general disorders and administration site conditions, injury, poisoning, renal and urinary disorders, hepatic disorders and skin and subcutaneous tissue disorders. Some of these have been addressed above.

Diarrhea was a commonly reported AE. In the phase 1 studies, diarrhea was reported by 5.0% of subjects who received dalbavancin and in the phase 2/3 studies, diarrhea was reported by 5.6% of dalbavancin-treated patients. Several other AEs were reported that may be consistent with **C. difficile diarrhea**, such as antibiotic-associated colitis (reported by 2 [0.2%] dalbavancin-treated patients), clostridium colitis (reported by 1 [0.1%] dalbavancin-treated patient), and colitis pseudomembranous (reported by 1 [0.1%] dalbavancin-treated patient). All of these AEs except for 1 case of antibiotic-associated colitis was considered to be possibly related to study drug.

For phase 1 studies, adverse events reported as **general disorders and administration site conditions** were as follows: infusion site pain 2.8% (reported by 4 subjects receiving dalbavancin), infusion site erythema 1.4% (2 subjects), injection site erythema 0.7% (1 subject) and infusion site rash 0.7% (1 subject). Additionally, there was one subject (13-001-020), who had a mild allergic reaction which included facial flushing.

In phase 2/3 studies, infusion site-associated AEs were more frequently reported by patients who received a comparator than those who received dalbavancin. 25 (3.5%) patients who received dalbavancin and 27 (4.7%) patients who received a comparator had at least 1 infusion site-associated. The most frequently reported infusion site-associated AE was infusion site reaction, reported by 0.8% of dalbavancin-treated patients.

With regard to the **skin and subcutaneous tissue disorders**, there were no cases of Red Man syndrome or anaphylaxis in any dalbavancin- treated patient. Twenty nine subjects (2.6%) reported rash as AE, 16 (1.4%) of them were considered related to dalbavancin.

In spite of this, intravenous administration of dalbavancin was associated with immediate infusion reactions in dogs. Although these effects were transient and most likely related to histamine release, the applicant is asked to further discuss this issue.

Adverse events compatible with "Red Man syndrome" and adverse events possibly associated with a systemic response to study drug administration have been analysed by the applicant. Results showed similar proportion of adverse events related to hypersensitivity for Dalbavancin and the comparators group. The RMP has been updated accordingly.

The long half-life of dalbavancin is considered as a potential concern in relation to allergic reactions. The MAH is supporting investigator research into techniques utilising continuous renal replacement as a possible method to remove dalbavancin from patients experiencing severe adverse events, if this should ever prove necessary.

Risk Management Plan

The Applicant has submitted a Risk Management Plan (version 1.1), including the requested parts in the RMP guideline document. This document has been updated accordingly to the comments done in the previous assessment.

CHMP's general comments on the RMP:

Altough new information has been included no information related to comparators used in clinical trials can be found through the document. The applicant is reminded that the RMP is to be read as a stand-alone document, and that concepts like "comparator" should be explain. The applicant must also go through the document, especially section 2.3 Detailed action plan for identified risks – where the copy-and-paste function seems to have been used too eagerly (see e.g. 2.4.2 Hepatobilary disorders, where it is stated that (…) Events related to **dysglycemias** will be monitored as targeted medical events.- Such mistakes are made repeatedly in this section.)

The applicant has only suggested routine pharmacovigilance activities. The rapporteurs are of the opinion that prescription monitoring study should be performed to study off-label use and the use in children. In addition follow-up questionnaires should be made available for specific follow-up of all spontaneous reports of ADRs that are listed in the summary of safety concerns (i.e. all identified or potential risks). The aim of such questionnaires being to obtain as complete information as possible on ADRs of special interest.

Potential for overdose:

The applicant has stated that there is a potential for over-dosage, as the product has a two-step dilution process. In light of the long half-light and lack of knowledge on how to manage over-dosage, it seems crucial to avoid wrong handling (lack of dilution) of the product. The CHMP therefore suggest including pictograms in the labelling/product information which clarify the dilution process. This is a routine risk minimisation activity.

In general, most of the important identified risks have now been included in the RMP. The important identified risks mentioned in the Safety Specification are now more consistent with the Clinical Safety evaluation. The applicant has added the information relevant to the safety of the product as discussed in detail in the safety section above. Based on the new completed safety specifications, the whole RMP has been updated accordingly. The following safety concerns have been added as important potential or identified risks into the RMP: ear and labyrinth disorders, myelosuppression (only anemia included), hypersensitivity, pseudomembranous colitis, nephrotoxicity and arrhythmia (only QT-prolongation included). "Potential of emergence of resistance" has been moved into important identified risks.

The CHMP find that the following risks, discussed as potential risks by the applicant, should be moved to the Identified risks section: Hypersensitivity, Anaemia and Off-label use. Hypersensitivity and Anaemia has been reported in dalbavancin treated patients. They are therefore to be regarded as

identified risks. When it comes to off-label use, the applicant has estimated 30-40 % off-label use, and off-label use should consequently be regarded as an identified risk.

In addition other effects belonging to the SOC Blood and lymphatic system disorders, such as Platelet disorders (HLGT), Red blood cell disorders (HLGT) and White blood cell disorders (HLGT) should be included among the safety concerns. Haematological adverse events are associated with gyclopeptides, and are a potential class effect. Adverse events belonging to these HLGTs are reported for dalbavancin.

In the CHMP's view nephrotoxicity in itself, not limited to patients with an impaired renal function, should be included as a potential risk.

Related risks of lack of efficacy and off-label use, especially the potential safety profile during the long-term treatment with this long-half-life-product, should be included into potential risks and monitored via routine pharmacovigilance as proposed in the RMP.

The Applicant has updated the RMP to include "Off-Label Use" as a potential risk. The applicant states that "lack of efficacy" is not related to safety and that the in vitro surveillance programs are enough to cover the potential lack of efficacy from a safety point of view. This can be agreed. However, the applicant is requested to include in the RMP to follow-up reports of lack of efficacy in the context of emergence of resistance or off-label use, specifically.

Section "non-clinical safety specification" has been updated to include immunotoxicity (sign. decrease of humoral immune response observed in male rats) and impairment of male fertility.

For each important identified or potential risk or missing information, the action plan includes passive surveillance (routine pharmacovigilance and expedited reporting) and discussion of adverse events in PSUR. For some of the specific safety concerns additional data may be obtained from ongoing clinical trials (active surveillance).

Additional new data are also expected from the routine pharmacovigilance activities. It is stated that the aggregate information generated would be reviewed on a periodical basis and summarized at the time of the PSUR submission.

A summary table of safety concernsis included below:

Table 79. Summary of Safety Concerns

Important identified risks	Emergence of Resistance Pseudomembranous colitis
Important potential risks	Dysglycaemia Hepatobiliary disorders QT Prolongation Ear and Labyrinth disorders Anaemia Hypersensitivity Nephrotoxicity in patients with impaired renal function Off-Label Use
Important missing information	Paediatrics Pregnant and lactating women

Overall, the CHMP considers that the RMP as proposed by the applicant is a better approach than the previous version. The applicant has followed most of the comments made in the previous assessment. However, there are particular concerns that need to be revised in view of the responses given to the list of outstanding issues, e.g. nephrotoxicity.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

V.1 Clinical context

Bacterial infections of the skin and underlying soft tissues are one of the most common infections in patients visiting emergency room clinics in both hospitals and office based practices.

Studies on the effect of antibiotics in SSTI need to be well defined with documentation of both local and systemic signs of infection. Infections immediately treated with incision and drainage is less suitable for studies and one or more signs of systemic infections should be required (European guidelines for clinical evaluation of anti-infective drug product 1993. European Society of Clinical Microbiology and Infectious Diseases; Stevens DL & al., 2005). Furthermore, it is important that the type of infection is well characterized. The validity of the results requires also that a significant number of each type of infection is included and preferably separate analyses should be made if abscesses, burn wound infections and necrotizing fasciitis are included.

In the setting of continuing emergence of resistance among Gram-positive pathogens worldwide, there is an increasing medical need for new antibacterial agents with enhanced Gram-positive activity. While *S. pyogenes* remains susceptible to penicillins, the emergence of resistance to all beta-lactam antibiotics in *S. aureus* raises a tremendous threat to public health. Glycopeptides such as vancomycin and teicoplanin were the only available options for treating most serious infections due to methicillin-resistant strains; however, concerns over increases in the rates of heteroresistance and tolerance to vancomycin, combined with its pharmacodynamic and clinical shortcomings and the increasingly important role of grampositive bacterial infections in the clinical setting, have motivated the development of newer agents. Dalbavancin, a lipoglycopeptide antibiotic, is a teicoplanin derivative that *in vitro* presents improved features respect to classical glycopeptides.

V.2 Benefits

Dalbavancin has an antibacterial spectrum which includes most species of Gram-positive bacteria, in particular those that are implicated in SSTI. The in vitro potency of dalbavancin, with a MIC90 ranged from ≤ 0.03 to 0.12 mg/L for most species (including *S.aureus* and streptococci), was mostly equal to or greater than that of comparators, including vancomycin, teicoplanin, linezolid and quinupristin/ dalfopristin. The activity of dalbavancin against some resistant Gram-positive pathogens, especially against methicillin-resistant *S. aureus*, is considered as a benefit.

This application is based primarily on the results from one single pivotal clinical trial, VER001-9. The primary efficacy analysis, clinical response in the clinically evaluable population at TOC, suggested that dalbavancin is as efficacious as linezolid in the treatment of cSSTI. However, the reliability of the conclusion of non-inferiority based on this study is questioned due to the following issues:
Based on the inclusion criteria, it is difficult to decide to what extent the subjects had infections of adequate severity to require i.v. antibiotic therapy. Thus, the study population may not be representative for the population for which dalbavancin is intended. The inclusion criteria in effect did not require the presence of at least 1 sign of systemic infection. This criterion is considered to be critical for the characterisation of a population with complicated disease. Furthermore it seems that approximately 25-30% of the patients included neither had fever, leucocytosis or bandemia. Apparently, many of these patients did not have any other systemic signs of infection which could justify for inclusion. Furthermore, a classification of the severity of the infection has not been performed. This makes it difficult to determine how many patients enrolled at baseline could be characterised as having severe infection and were in actual need of i.v. antibiotic treatment.

The most striking property of dalbavancin is probably its very long elimination half-life, which allows for the once a week dosing schedule. The long half-life, on the other hand, caused some difficulties with the timing of the TOC as it quite likely that at this time there is still a significant plasma concentration of dalbavancin. A later follow up visit could have been valuable to verify the results at TOC, however, the late follow up in this case was a telephone call, not a regular visit.

Three additional studies have been conducted, one in cSSSI, a second one in mixed c/uSSSI and a third one in catheter-related bacteriemic patients. None of these studies can be regarded as providing pivotal evidence of efficacy.

V.3 Risks

Overall, the safety profile of Dalbavancin is the one expectable for a glycopeptide antibiotic.There was no apparent safety issues for which dalbavancin were markedly worse than the comparators. For a few organ systems, however, there are concerns or perhaps uncertainties with regard to the “true” toxicity of dalbavancin. These include potential nephrotoxicity, toxicity of the drug in patients with severe renal impairment, effect on cardiac repolarisation and and skin associated adverse events. None of these uncertainties are by themselves precluding the potential approvability of the drug, though they should be further studied and considered in the RMP.

The long hal-life of dalbavancin makes the handling of severe allergic reactions and other severe treatment-related adverse events, where immediate stopping of the treatment is a pillar of the handling of such diseases, difficult. In addition, the long-term effects of dalbavancin regarding the potential for resistance development due to the exposure to low concentrations of dalbavancin over an extended time period also remain to be elucidated. For the time being, none of these concerns have been adequately addressed. Although these could potentially be solvable through adequate post-marketing measures, further information has been requested.

The RMP as proposed is a good approach, but there are particular potential risks which require a much more extensive discussion and risk minimisation activities need to be revised in the light of the updated Safety Specification and the applicant’s response to the List of Questions.

V.4 Balance

The results of the pivotal trial indicate that dalbavancin is non-inferior to linezolid in patients with cSSTI. However, several methodological weaknesses of the pivotal trial question the validity of the results. These weaknesses pertain to the following issues: the potential bias in favour of dalbavancin at TOC, the lack of high quality data at LFU to support the TOC-data, the inability to provide separate rates for cure and improved, and the fact that for a broad indication like cSSTI clinical efficacy has only been proven for S. aureus and to a relatively large degree this is based on one single clonal CA-MRSA ourbreak in the US. Furthermore, according to the population actually enrolled, it is questionable whether patients included in the single pivotal trial are properly representing a population in need of antibiotic therapy, especially intravenous therapy. To some extent, this kind of hindrances could be handled through SPC warning highlighting the limitations of the clinical database. However, in this case, the above mentioned problem needs to be jointly considered with the fact that this application is based on a single pivotal trial of which the quality may be questioned. Altogether, these issues highlight the need to discuss whether further confirmatory evidence of the efficacy of dalbavancin in a well-defined population of cSSTI should be requested before approval.

The safety of dalbavancin is not essentially dissimilar to other antibiotics of the same class. Further issues warranting additional investigation have been identified. However, none of them are considered by themselves to preclude a marketing authorisation.

V.5 Conclusions

The overall B/R of Exulett remains negative