18 December 2014
EMA/39820/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xydalba

International non-proprietary name: dalbavancin

Procedure No. EMEA/H/C/002840/0000

Note

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

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List of abbreviations

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
AUC	area under the concentration time curve
$AUC_{0\text{-Day }7}$	Area under the plasma concentration-time curve extrapolated through Day 7
AUC0-inf	Area under the plasma concentration-time curve extrapolated through infinity
BSA	body surface area
CE	clinically evaluable
CI	confidence interval
CL	clearance
CPMP	Concept Paper on the Development of a Committee for Proprietary Medicinal Products
CRBSI	Catheter-related bloodstream infections
CrCl	creatinine clearance
cSSTI	complicated skin and soft tissue infection
ECG	electrocardiogram
EOT	end-of-treatment visit
ESRD	end-stage renal disease
EU	European Union
FDA	US Food and Drug Administration
IDSA	Infectious Diseases Society of America
ISS	Integrated Summary of Safety
ITT	intent-to-treat population
IV, i.v	intravenous
LFU	late follow-up visit
MAG	mannosyl aglycone
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
MicroITT	microbiological intent-to-treat population
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NDA	New Drug Application
PCS	potentially clinically significant

PD	pharmacodynamic
PK	pharmacokinetic
PPK	population pharmacokinetic
q4h	every 4 hours
q6h	every 6 hours
q12h	every 12 hours
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SD	standard deviation
SFU	short-term follow-up visit
SOC	System Organ Class
SSI	surgical site infection
SSTI	skin and soft tissue infection
t > MIC	time-dependent attainment of free drug concentrations above the MIC
$t_{1/2}$	half-life
TOC	Test-of-cure visit
TEAE	treatment-emergent adverse event
uSSTI	uncomplicated skin and soft tissue infection
V_1	volume of distribution on the central compartment
VISA	vancomycin-Intermediate *Staphylococcus aureus*
V_{ss}	steady-state volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Durata Therapeutics International B.V. submitted on 27 November 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Xydalba, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 December 2012.

The applicant applied for the following indication: treatment of complicated skin and soft tissue infections (cSSTI) in adults when known or suspected to be caused by susceptible strains of Gram-positive bacteria, including the treatment of bacteraemia associated with these infections.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Dalbavancin was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0245/2013 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0245/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance Dalbavancin HCL contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 16 December 2010 and 19 January 2011. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Dalbavancin has been given a Marketing Authorisation in United States on 23 May 2014.

1.2. Manufacturers

Manufacturer responsible for batch release

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Co Armagh
BT63 5UA
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson

Co-Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 27 November 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2014.
- PRAC Rapporteur RMP Assessment Report was adopted by PRAC on 10 April 2014.
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 September 2014.
- PRAC Rapporteur RMP Assessment Report was adopted by PRAC on 11 September 2014.
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 17 November 2014.
- The Rapporteurs Joint Assessment Report was circulated to all CHMP members on 26 November 2014.

- PRAC Rapporteur RMP Assessment Report was adopted by PRAC on 4 December 2014.
- During the meeting on 18 December 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Xydalba.

2. Scientific discussion

2.1. Introduction

Skin and soft tissue infections (SSTI) are among the most common infections in both hospitals and community settings, and remain a significant source of morbidity and mortality. These infections can range in severity from uncomplicated skin and soft tissue infections (uSSTIs), such as simple folliculitis, to complicated skin and soft tissue infections (cSSTIs), including very serious conditions such as necrotizing fasciitis and Fournier's gangrene. Complicated skin and soft tissue infections involve deeper soft tissue than uncomplicated infections, and may require significant surgical intervention and parenteral antibiotic therapy. 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. 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.

Systemic risk factors which predispose patients to severe forms of SSTI include diabetes mellitus, malnutrition, immune deficiencies, sensory neuropathies, chronic systemic illness, high age and smoking.

The pivotal studies supporting this application enrolled patients who complied with the definition of the term “acute bacterial skin and skin structure infections (ABSSSI)”, which practically encompasses patients with cellulitis/erysipelas, wound infections and major cutaneous abscesses with a lesion area size of at least 75 cm^2 (possibly lower for areas that involve certain body surface sites, such as the face). The CHMP was of the opinion that the use of this term was more appropriate than cSSTI, as it better described the patient populations enrolled in the clinical trials. The applicant agreed with this conclusion. In this report, the two terms are however used interchangeably.

Studies on the effect of antibiotics 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.

Although skin and soft tissue infections include a vast array of clinical entities, they are most often caused by two single microorganisms, *Staphylococcus aureus* and *Streptococcus pyogenes*.

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. In recent years methicillin-resistant *S. aureus (*MRSA) has become a major concern, not just with respect to nosocomial infections, but also because a community-acquired (CA) variant has

appeared, unrelated to the hospital acquired strains. Glycopeptides such as vancomycin and teicoplanin are often the choice of drug 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, have motivated the development of newer agents.

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 disruption of the cell wall results in bacterial cell death. Dalbavancin is active against important groups of Gram-positive bacteria, including strains of methicillin resistant *Staphylococcus aureus* (MRSA) and some *S. aureus* with reduced susceptibility to glycopeptides (GISA). Its potent *in vitro* activity has been substantiated in various animal models of infection and it possesses a pharmacokinetic (PK) profile which allows once-weekly intravenous (IV) dosing.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing dalbavancin hydrochloride as active substance equivalent to 500 mg of dalbavancin.

Other ingredients are: mannitol (E421), lactose monohydrate, hydrochloric acid and sodium hydroxide.

The product is available in single-use 48 ml type I glass vials with an elastomeric stopper and a flip off seal.

2.2.2. Active Substance

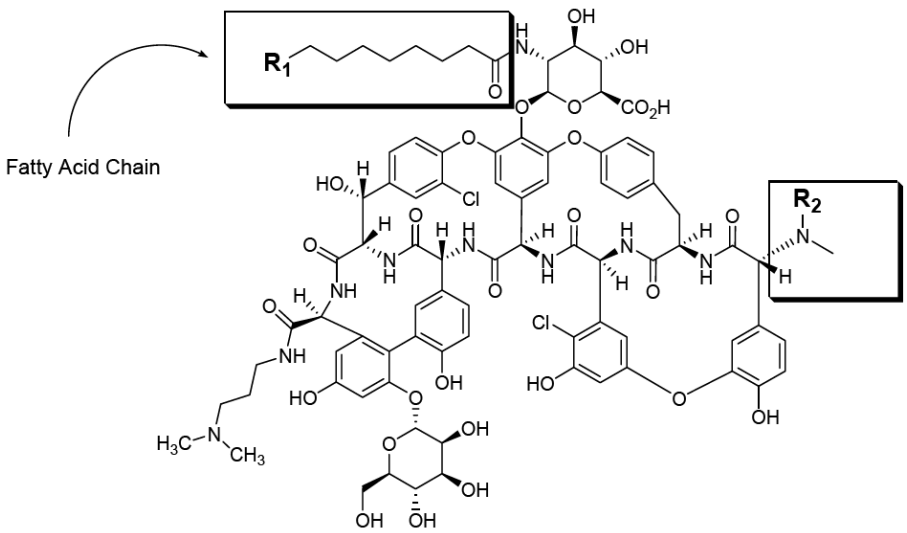
General information

Dalbavancin is a semi-synthetic cyclic lipoglycopeptide antibiotic consisting of a mixture of five closely related homologues that can be grouped into two structural families, designated dalbavancin A and dalbavancin B. The dalbavancin A familyconsists of two subtypes: dalbavancin A_0 and A_1. Dalbavancin B, is comprised of three subtypes: B_0, B_1, and B_2.

These homologues share the core structure and all have the same stereochemistry. They differ from one another primarily in the length and/or branching of their respective fatty acid side chains on the N-acylaminoglucuronic acid moiety (designated as R_1) and/or the presence of an additional methyl group (designated as R_2) on the terminal amino group.

Dalbavancin drug substance is a hydrochloride salt.

The structure and chemical IUPAC name of the homologues are:



Homologue	R_1	Number of carbons R_1	R_2
A_0	$CH(CH_3)_2$	3	H
A_1	$CH_2CH_2CH_3$	3	H
B_0	$CH_2CH(CH_3)_2$	4	H
B_1	$CH_2CH_2CH_2CH_3$	4	H
B_2	$CH_2CH(CH_3)_2$	4	CH_3

Dalbavancin A_0 : 2-deoxy-1-O-[(3S,15R,18R,34R,35S,38S,48R,50aR)-5,31-dichloro-38-{[3-(dimethylamino)propyl]carbamoyl}-6,11,34,40,44-pentahydroxy-42-(α-D-mannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaoxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-1H,15H,34H-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano) 4,8:10,14:25,28:43,47-tetrametheno[1,14,6,22]dioxadiazacyclooctacosino[4,5-m][10,2,16] benzoxadiazacyclotetracosin-56-yl]-2-[(9-methyldecanoyl)amino]-β-Dglucopyranuronic acid.

Dalbavancin A_1: 2-deoxy-1-O-[(3S,15R,18R,34R,35S,38S,48R,50aR)-5,31-dichloro-38- {[3-(dimethylamino)propyl]carbamoyl}-6,11,34,40,44-pentahydroxy-42-(α-D-mannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaoxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-1H,15H,34H- 20,23:30,33-dietheno-3,18:35,48 bis(iminomethano)4,8:10,14:25,28:43,47-tetrametheno[1,14,6,22]dioxadiazacyclooctacosino[4,5-m][10,2,16] benzoxadiazacyclotetracosin-56-yl]-2-(undecanoylamino)-β-Dglucopyranuronic acid.

Dalbavancin B_0: 2-deoxy-1-O-[(3S,15R,18R,34R,35S,38S,48R,50aR)-5,31-dichloro-38- {[3-(dimethylamino)propyl]carbamoyl}-6,11,34,40,44-pentahydroxy-42-(α-D-mannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaoxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-1H,15H,34H-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano) 4,8:10,14:25,28:43,47-tetrametheno[1,14,6,22]dioxadiazacyclooctacosino[4,5-m][10,2,16] benzoxadiazacyclotetracosin-56-yl]-2-[(10-methylundecanoyl)amino]-β- D-glucopyranuronic acid.

Dalbavancin B_1: 2-deoxy-1-O-[(3S,15R,18R,34R,35S,38S,48R,50aR)-5,31-dichloro-38- {[3-(dimethylamino)propyl]carbamoyl}-6,11,34,40,44-pentahydroxy-42-(α-D-mannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaoxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-1H,15H,34H-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)- 4,8:10,14:25,28:43,47-tetrametheno[1,14,6,22]dioxadiazacyclooctacosino[4,5-m][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-(dodecanoylamino)-β-Dglucopyranuronic acid.

Dalbavancin B_2: 2-deoxy-1-O-[(3S,15R,18R,34R,35S,38S,48R,50aR)-5,31-dichloro-38- {[3-(dimethylamino)propyl]carbamoyl}-6,11,34,40,44-pentahydroxy-42-(α-D-mannopyranosyloxy)-15-(dimethylamino)-2,16,36,50,51,59- hexaoxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro- 1H,15H,34H-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)- 4,8:10,14:25,28:43,47-tetrametheno[1,14,6,22]dioxadiazacyclooctacosino[4,5-m][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronic acid.

Dalbavancin exhibits stereoisomerism due to the presence of 18 chiral centres. The configuration of the asymmetric carbons is controlled by the microorganism in the fermentation process. The core structure of the active substance has been elucidated by elemental analysis and spectroscopic techniques (IR, UV, MS and ^{1}H- and ^{13}C NMR) and powder X-ray diffraction.

Polymorphism has not been observed for dalbavancin.

The active substance is a white to tan hygroscopic amorphous solid. It is insoluble in acetone; freely soluble in water (with higher solubility at pH ≤ 5.5), dimethylsulfoxide and dimethylformamide; practically insoluble in chloroform, n-butanol and n-octanol; and soluble in methanol.

Manufacture, characterisation and process controls

Dalbavancin is a semi-synthetic cyclic lipoglycopeptide manufactured by fermentation of a selected strain of *Nonomuraea* species followed by chemical modification.

The fermentation steps comply with the Ph. Eur. monograph on “Products of fermentation”. The process has been described in sufficient detail covering primary and secondary seeds, primary fermentation, microfiltration, deacetylation, and purification. The absolute chirality of the intermediate and therefore dalbavancin’s chirality, is controlled by the microorganism in the fermentation process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities have been well discussed with regards to their origin and characterised. All impurities observed above the reporting threshold of 0.10% have been identified.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC), component distribution (HPLC), related substances (HPLC), microbial limit (Ph. Eur.), bacterial endotoxins (Ph. Eur.), residual solvents (GC), pH (Ph. Eur.), water content (KF), chloride content (potentiometry), heavy metals (ICP-MS), and residue on ignition (Ph. Eur.)

The Guideline on Setting Specifications for Related Impurities in Antibiotics (EMA/CHMP/CVMP/QWP/199250/2009) has been followed.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Batch analysis data on several pilot scale and 6 commercial scale batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 7 commercial-scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 48 months under long term conditions at -20°C±5°C, and for up to 6 months under accelerated conditions at 5 ºC according to the ICH guidelines were provided. In addition, stability data from 3 commercial scale batches stored at 25°C/60% RH have been submitted.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results from forced degradation studies under basic, acid, oxidative and heat conditions were also provide on one batch.

The following parameters were tested: appearance, assay, component distribution, related substances, water content, pH and microbial limits.

The analytical methods used were the same as for release and were stability indicating.

No trends were observed for any of the parameters tested in the batches stored at -20 ºC, and all results remained within the proposed specification. A decrease on assay and increase on related substance levels was observed at 5 ºC, but all results were within the predefined specifications during 6 months. However, after 6 months at 5 ºC, and under storage at 25 ºC/60% RH, some parameters were outside of the predefined specification.

The photostability study showed that dalbavancin is susceptible to light, but is adequately protected by the primary packaging.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the pharmaceutical development was to develop a sterile intravenous formulation containing dalbavancin hydrochloride as active substance and since the main degradation pathway for dalbavancin involves hydrolysis, a solution formulation was not feasible and the development focused on the development of a lyophilised dosage form.

The solubility and stability of dalbavancin at different pH were evaluated in order to determine the optimal pH of the formulation.

During early development, two drug product strengths, 200 mg/vial and 250 mg/vial (varying only in fill volume), were used in clinical trials (Phase 1, Phase 2 and the first three Phase 3 studies). As development progressed, based upon the therapeutic dosing requirements, formulation development focused on the

improvement of the dosing convenience (by producing a 500 mg/vial) and the enhancement of the long-term stability of the finished product. This 500 mg/vial formulation was utilised for all Durata clinical trials, including two pivotal Phase 3 studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The choice of sterilization method was adequately justified.The primary packaging is single-use type I glass vial with an elastomeric stopper and a green flip off seal. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and compatibility with the formulation has been demonstrated with extraction and leachable studies.

Dalbavancin finished product requires two preparatory steps prior to administration: reconstitution with sterile water for injection to form the reconstituted product, and subsequent dilution with an appropriate diluent prior to infusion. A compatibility screening study with different diluents was conducted. Based on the results of this study, 5% glucose is the recommended diluent for this formulation. This diluted infusion is chemically and physically stable at room temperature (20 to 25 °C) and under refrigerated conditions (2 to 8 °C) for at least 48 hours after reconstitution. The use of sodium chloride should be avoided as it caused precipitation of dalbavancin when used at 9 mg/ml. The finished product is not physically compatible with Lactated Ringer's solution for infusion, and 5% glucose in Lactated Ringer's solution for infusion. The compatibility of dalbavancin with 5% glucose with 0.45% sodium chloride and other intravenous substances, additives, or medications has not been established.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: dissolution of dalbavancin and pH adjustment, sterile filtration, aseptic filling, lyophilisation and packaging. The process is considered to be a non-standard process.

Major steps of the manufacturing process have been validated at commercial scale by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form description (lyophilised and reconstituted), identification (IR, HPLC), reconstitution time, constituted solution clarity (Ph. Eur.), assay (HPLC), drug components (HPLC), related substances (HPLC), water content (Ph. Eur.), pH (Ph. Eur.), uniformity of dosage units (weight variation) (Ph. Eur.), sterility (Ph. Eur.), particulate matter (Ph. Eur.) and bacterial endoxotins (Ph. Eur.).

Batch analysis results from 6 batches manufactured at the proposed commercial manufacturing site confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification have been provided.

The proposed limits for the drug components (homologs A_0, A_1, B_0, B_1, and B_2) are well in agreement with the batch results presented, and can be accepted considering the limited manufacturing experience at the time of opinion and the similarity of the different homologs. However, as these limits are wider than the levels obtained in the clinical batches, the applicant is recommended to revise these limits when additional data have been generated.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of 3 pilot scale and 3 commercial scale batches of finished product stored under long term conditions for up to 24 months at 25 ºC / 60% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Additional supportive stability data from 3 pilot scale batches and stored for 36 months at 5°C, for up to 42 months at 25°C/60% RH, for up to 18 months at 30°C/65% RH and for 6 months at 40°C/75% RH were submitted.

Samples were tested for description (solid and reconstituted solution), constituted solution clarity, assay, component distribution, impurities, reconstituted time, pH, water content, particulates, sterility and reconstituted stability. The analytical procedures used are stability indicating.

The results from these studies complied with the proposed specifications.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. All results remained within the predefined specification limits.

An in-use stability testing was performed on batches of dalbavancin finished product after reconstitution with water for injection to a final concentration of 20 mg/ml the vials were stored at 5 ºC and 30 ºC / 75 % RH for 48 hours and tested for assay, degradation products, solution clarity, pH of reconstituted solution and particulate contamination. The results indicate that reconstituted dalbavancin powder for solution for infusion is stable when stored for 48 hours at 5 °C or 30 °C/75 % RH.

In addition, dalbavancin finished product was reconstituted with sterile water for injection and further diluted with 5 % glucose into infusion bags. Samples were evaluated for appearance, pH, potency/purity at initial (room temperature 20 to 25 °C), 24 hours (room temperature) and 48 hours (ambient and refrigerated conditions). The diluted infusion was shown to be chemically and physically stable at room temperature (20 to 25 °C) and under refrigerated conditions (2 to 8 °C) for at least 48 hours after reconstitution.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

A valid TSE CEP for a component used in the manufacturing of the active substance has been provided.

It is confirmed that lactose and other relevant components used in the manufacturing of the active substance are produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of

important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant is recommended to revise the limits for the drug components (homologs A_0, A_1, B_0, B_1, and B_2) in the finished product specification once additional batch analysis data have been generated.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal toxicology and safety pharmacology studies were performed according to Good Laboratory Practice (GLP).

2.3.2. Pharmacology

Primary pharmacodynamic studies

For primary Pharmacology and Pharmacokinetic/pharmacodynamic relationships please see the clinical part of the CHMP AR.

Secondary pharmacodynamic studies

Secondary pharmacodynamic effects of dalbavancin may not be expected since dalbavancin specifically inhibits bacterial cell wall synthesis via interaction with the bacterial cell wall components and since similar peptidoglycan components are not found in eukaryotic cells. However, a broad *in vitro* screening of 120 receptors, ion channels, transporters and enzymes revealed several targets with IC_{50} values that were below the plasma C_{max} levels obtained in clinical studies (C_{max} = ~250-300 µg/mL (165 µM)). Even though plasma levels declined rapidly the levels still reached ~55 µM 12 hours and ~10 µM 13 days after a single IV dose of 1000 mg infused over 30 min and the clinical 1000/500 mg weekly regimen may give plasma levels higher than 20 µM (~40mg/L) for ~14 days. Due to the short $t_{1/2}$ alpha phase for dalbavancin, it is agreed that C_{avg}, and not only C_{max}, is relevant in this context and the estimated K_i/IC_{50} levels are approximately ≥2-fold the C_{avg} for all secondary pharmacological targets identified.

An overview of data on expression, physiological function, and known agonists/antagonists, for the secondary pharmacological targets where an IC_{50} level less than 2-fold the human unbound C_{max} for dalbavancin has been identified (e.g. the glucocorticoid receptor, caspase-3, ACE, CaMK2alpha, FLT-1, and P38alpha) revealed no specific concerns. CaMK2alpha is the target where the lowest IC_{50}/C_{avg} ratio has been identified (1.9), raising a potential cause for concern related to interference within in the CNS in particular. The applicant refers to clinical data from 2 patients where dalbavancin levels in the CSF were below LoQ. Although limited, these data are considered useful and reassuring. Furthermore, a review of the Phase 2/3 integrated safety database has not revealed any specific drug-drug interactions in dalbavancin-treated subjects, or a safety profile different from the comparators.

Safety pharmacology programme

The cardiovascular, respiratory, CNS and autonomic nervous system safety of dalbavancin was evaluated according to guidelines at doses above or equal to the human dose. No effect was seen on the central nervous system (Irwin screen and body temperature in mice), autonomic nervous system (cardiac baroreflex function in rats) or respiratory function (respiratory parameters in rats) at doses up to 20 mg/kg IV. Plasma exposure at these single dose administrations is expected to have been substantially lower than expected human clinical exposure. However, based on the available clinical safety data this is not considered to be critical.

Possible cardiovascular effects of dalbavancin was studied *in vitro* (no effect on hERG at 16.9 µg/mL, ~equal to human fu plasma C_{max} level and inconclusive study with rabbit Purkinje fibres) and in several *in vivo* studies. An intermittent non-dose-dependent decline in blood pressure and small increase in heart rate occurred during or immediately after infusion of dalbavancin at doses ≥30 mg/kg in dogs. These hemodynamic changes were associated with hives, skin swelling and erythema, indicating a possible involvement of histamine release. Doses greater than 30 mg/kg in dogs resulted in C_{max} values greater than the ~300 µg/mL observed in clinical trials. The C_{max} (1492 mg/L) of the 60 mg/kg dose session was almost five times the clinical C_{max}. The cumulative AUC_t (25,242 mg·h/L) for the 40 mg/kg dose session approximated the AUCt (26,000 mg·h/L) for the clinical dose. Total cumulative exposure in this study (87,528 mg·h/L) was >3 times that for the clinical dose. Similar hemodynamic effects have occasionally been reported in human clinical trials of dalbavancin, including a single case of bronchospasm/anaphylactoid reaction.

A dose-dependent antiplatelet effect on collagen induced aggregation was seen *in vitro* in rabbit plasma but no statistically significant effect on bleeding time was detected *in vivo* in rat, suggesting that the detected *in vitro* effect is not likely to be of clinical relevance.

2.3.3. Pharmacokinetics

Clearance and volume of distribution of dalbavancin scale allometrically by species body weight. Concentrations and exposures were dose proportional within species and long residence times were observed in all species investigated. Volume of distribution was approximately 0.2 L/kg (similar to the extracellular water volume) indicating an interstitial distribution of dalbavancin.

Dalbavancin was widely distributed throughout the body and was slowly cleared from all of the 40 tested tissues and organs in rats administrated ^{3}H-dalbavancin. Concentrations and half-lives of drug-derived radioactivity in most tissues of rat were comparable to that observed in plasma over a period of 70 days, suggesting that the drug is well-distributed, in equilibrium between tissues and plasma, and do not accumulate substantially in any specific tissue/organ. Low but detectable concentrations of drug-derived radioactivity were found in the CNS. It may be noted that tissue concentrations in some tissues (e.g. adrenals, spleen and lymph nodes) seemed to have a longer half-life compared to plasma. A possible accumulation of dalbavancin in these tissues after repeat dose administration can thus not be excluded, which also might be a contributing factor for the histopathological changes seen in dogs in adrenals, spleen and lymph nodes after prolonged administration and also after

recovery (see repeat dose toxicology). However, no such histopathological changes were reported for rat. Considering the administration of only two doses to humans, one week apart, possible accumulation and related histopathological changes are not likely to be of relevance for the human situation.

In dogs, dalbavancin clearance from the liver after a single dose in a mass balance study was slower than in rats. However, qualitatively the distribution of drug-derived radioactivity within the liver was the same for rats and dogs. In rats and minipigs, dalbavancin penetrated the skin with concentrations above pharmacological target levels. Plasma protein binding was high and were similar across species (94.16±0.43 in rat; 93.06±1.46 in dog and 92.60±1.58 in human plasma). For both rats and dogs, the ratio of blood to plasma concentrations of drug-derived radioactivity was constant and <1 throughout 70 and 42 days, respectively.

Dalbavancin can be characterized as a cationic amphiphilic drug, and evidence from mass balance studies suggest that it preferentially distributes to tissues with high phospholipid content (e.g., kidney, liver) and in vitro incubation of a mouse macrophage cell line with ^{14}C-dalbavancin showed that most of the cell-associated radioactivity was membrane associated rather than cytoplasmic. Based on radiolabeled mass balance studies in rats and dogs, dalbavancin is relatively slowly released from these tissues, which may contribute to the extensive terminal $t_{1/2}$ of the drug.

Because of dalbavancin's long residence time, estimates of terminal $t_{1/2}$ across studies were highly dependent on assay sensitivity relative to the dosage administered and time elapsed between the dose and last quantifiable observation. The predominant $t_{1/2}$ values for drug-derived radioactivity were 14 and 24 hours in rats and dogs, respectively, as compared to an estimated terminal $t_{1/2}$ of ~26 days in both rat and dog and 16 days (range 14 to 17 days) in humans.

Dalbavancin was shown to be stable in vitro in incubations with rat, dog, and human liver microsomes, as well as in presence of rat, dog, and human hepatocytes. Hydroxydalbavancin (OH-dalbavancin), which was found in in vivo studies was not observed in liver microsomal or hepatocyte incubates. Only low or undetectable concentrations of OH-dalbavancin and mannosyl aglycone (MAG) were found in plasma, suggesting that the metabolite kinetics are formation rate limited, that is, the excretion rate constant is faster than formation rate constant. The biotransformation pathways of dalbavancin to its major metabolites, OH-dalbavancin and MAG have not been elucidated. It is thus not known if MAG is a “true” metabolite or not. However, based on the higher total amount of MAG in excreta as compared to the total amount administered via the batches used in studies in dog and rat, MAG is concluded to be formed in vivo via secondary biotransformation and/or chemical modification/degradation.

In rat and dog mass balance studies, radiochemical profiling was performed for urine, faeces, and plasma. All peaks in dog urine corresponded to either dalbavancin homologues already present in the drug substance or metabolites (OH-dalbavancin and MAG). Similar results were seen in human and dog urine profiled by LC/MS/MS and radioprofiled rat urine. Metabolites and intact drug are excreted in animal urine and intact drug is excreted in animal faeces (only very low levels of metabolites were found in faeces). Metabolite concentrations in human plasma were below or close to the limit of quantitation and similar results were observed in animals given clinically relevant doses. The presence of metabolites in excreta, especially within the first days after the dose, but not in plasma suggests that metabolites are rapidly eliminated. Plasma measures of dalbavancin-equivalent (radioactivity) and dalbavancin in mini-pig were similar, suggesting that radioactivity was associated with dalbavancin throughout the 4-week study and that no significant amounts of metabolites were formed, further supporting the metabolic stability of dalbavancin. Radiochemical profiling was also conducted on livers excised from rats and dogs administered ^{14}C-dalbavancin showed a majority of the radioactivity in the liver of rats associated with intact dalbavancin and no prominent metabolites.

Dalbavancin has dual routes of excretion, renal and faecal. In rat, 42%, 26%, and 10% of the drug-derived radioactivity was found in urine, faeces, and cage wash, respectively, over 120 days. Corresponding values from a dog mass balance study were 63%, 9%, and 5% over 70 days. Both intact dalbavancin and metabolites were excreted in these animal studies. In the rat and dog mass balance studies 80% and 90% of the administered radioactivity was recovered, respectively. Dalbavancin metabolites were eliminated primarily in urine. Hydroxydalbavancin excreted in urine over 70 days represented ~10% of the dose in rat and ~23% in dog. Minor amounts of MAG (~5% of the dose) were also found in urine. In rats, dogs, and humans the only major component found in faeces was dalbavancin. MAG and OH-dalbavancin together accounted for only minor amounts (~1%) of the dose in faeces. In rats, a comparison of drug-derived radioactivity in faeces and in bile showed that faecal excretion occurs by both biliary and non-biliary routes.

2.3.4. Toxicology

The toxicological profile of dalbavancin was evaluated in standard toxicology studies in mice, rats, dogs, rabbits and guinea pigs. Single dose toxicology studies in rats and mice and repeat dose toxicity studies up to 3 months in rats and dogs were performed. Reproductive and developmental toxicity studies were performed in rats and rabbits and included studies in juvenile rats. Based on the pharmacokinetic data and the similarity in metabolic profile between humans, rats and dogs together with the high metabolic stability of dalbavancin in all species investigated, the non-clinical species used are considered to be acceptable. Although a human mass balance study has not been performed a formation of an unknown human specific metabolite of significance for the toxicological evaluation of dalbavancin is considered to be highly unlikely.

The proposed dalbavancin clinical dosage regimen is a 1000 mg intravenous (IV) dose on Day 1, followed by a 500 mg IV dose one week later. In most nonclinical toxicology studies *in vivo*, dalbavancin was administered intravenously. Because of pharmacokinetic differences between animals and humans, daily dosing was performed in test animals for the duration of the treatment period in order to obtain sufficient exposures.

Single dose toxicity

Approximate LD_{50}-values after intravenous administration was approximately 200 mg/kg for both rat and mouse, while the estimated oral lethal dose was greater than 2000 mg/kg in both species. Adverse clinical signs included sedation/hypoactivity, shallow breathing, piloerection and clonic convulsions seen immediately after dosing. Recovery of clinical signs was seen within 24 h in surviving animals in mice and after 4-6 days in rats.

Repeat dose toxicity

In repeat dose toxicology studies (up to 3 months exposure) dalbavancin was shown to induce similar systemic toxicity in both rats and dogs with the main target organs being kidneys, liver and the haematological system. Local and systemic toxicological changes partially reversed in parallel with decreasing plasma dalbavancin concentrations and in proportion to the length of the recovery interval.

- Kidney

Renal toxicity was dose-dependent and evident at ≥20 mg/kg/day in 4-week studies and ≥10 mg/kg/day in 90-day studies in rats and dogs. Histopathological changes included dilatation, degeneration and necrosis of epithelial cells associated with regenerative basophilia, interstitial inflammation, and pigments in histiocytes. Increased blood urea nitrogen and creatinine levels, and findings of blood and epithelial cells in urine were also seen. The NOAELs for kidney were 10 mg/kg/day for 28 days of dosing and 5 mg/kg/day for 90 days of dosing. Renal toxicity was reversible, but residual renal fibrosis (also referred to as sclerosis) was observed after administration of doses higher than 40 mg/kg/day for more than 28 days. “Nephrotoxicity” is included as an “Important potential risks” in the RMP.

- Liver

Liver toxicity was also dose-dependent and evident at ≥40 mg/kg/day in 4-week studies and ≥10 mg/kg/day in 90-day studies in rats and dogs. Histopathological changes (e.g. hepatocellular centrilobular necrosis) were seen together with clinical chemistry changes (particularly increased AST and ALT, but also increased cholesterol, triglyceride, total bilirubin and GGT or decreases in albumin levels). The NOAELs for liver were 20 mg/kg/day for 28 days of dosing and 5 mg/kg/day for 90 days of dosing. Liver toxicity was reversible, but hepatic fibrosis was observed after administration of 40 mg/kg/day for 90 days in dogs. "Hepatic disorders" is included as an "Important potential risks" in the RMP.

- Haematological system

Several signs of haematological toxicity were observed in the repeated-dose toxicity studies in dogs (more pronounced) and rats with reduced RBC, haemoglobin, haematocrit and increased number of platelets in rats or decreased in dogs. In the 3-month toxicity study in dogs values for these haematological parameters were still affected after 2 month of recovery and did not reverse into baseline until an even more prolonged recovery. Haematological undesirable effects (anaemia, thrombocytosis, eosinophilia, leucopenia, neutropenia) are included as "uncommon adverse reactions" in the SmPC (section 4.8) and haematology effects are included as "important potential risks" in the RMP.

- Pigmentation

In addition, 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. However, there was no correlation to cellular damage or organ dysfunction and the presence of pigment vacuoles and/or dark pigment is interpreted as evidence of increased cell membrane turnover and accumulation of lipofuscin and not considered to be adverse. Findings diminished in incidence but did not completely reverse after recovery. Dalbavancin was shown not to be immunotoxic and a potential effect on macrophage function is thus not expected. The applicant concludes that these changes are attributed to tissue phospholipidosis as a consequence of the cationic amphiphilic structure of dalbavancin and its metabolites. However, since no histological analysis has been performed in order to identify phospholipidosis after treatment with dalbavancin there are no data to support this conclusion. This lack of data is not considered to be of any concern and no further studies are thus needed.

- Pancreas

The possibility of dalbavancin effect on endocrine pancreas was addressed during the previous submission and Glucose Homeostasis has been discussed by the applicant as part of this submission. Nonclinical toxicity studies up to 90 days duration in the dog and rat have shown no changes in serum glucose concentrations except in the study on juvenile rats in which a dose-dependent increase in plasma glucose was detected (20 and 40 mg/kg/day), although only in male rats. In the 90-day dog study there were no treatment-related findings of the pancreas of either the islets or acini while microscopic findings of vacuolization were observed at all doses (5, 10, and 40 mg/kg/day) in the 90-day rat study. There were no treatment-related findings in pancreatic islet cells in rats at any dose.

The vacuolization of acinar pancreas is not considered to be of relevance for a possible effect on glucose homeostasis, as also concluded during the previous assessment. In addition, based on the mild and reversible effects seen in the rat, the small and variable differences in GI-effects seen between dalbavancin and comparator treated patients in the clinic, and the limited duration of clinical administration of dalbavancin, the effects on the acinar pancreas seen in the rat are concluded likely to be of less clinical importance.

- Injection site

Local injection site toxicity was commonly seen in both rats and dogs characterized by macroscopic skin swelling and thickening at the injection site(s) that corresponded to microscopic perivascular inflammation and fibrosis and vascular degeneration/thrombosis. It may be attributed to local irritation related to extravasation of dalbavancin. In relation to the infusion, clinical signs of cutaneous swelling and/or erythema, particularly of the face and paws were seen in dogs, together with mucosal pallor, salivation, vomiting, sedation, and declines in

blood pressure and increases in heart rate, effects which may be attributed to histamine release. "Infusion-related reactions" is included as a warning in section 4.4 of the SmPC.

- Recovery

Local and systemic toxicologic changes partially reversed in parallel with decreasing plasma dalbavancin concentrations and in proportion to the length of the recovery interval. Renal and liver toxicity was reversible, but residual renal fibrosis (also referred to as sclerosis) was observed after administration of doses ≥40 mg/kg/day for ≥28 days and hepatic fibrosis was observed after administration of 40 mg/kg/day for 90 days in dogs.

NOAEL

The NOAELs for dogs are agreed to be 10 mg/kg/day after 28 days, and 5 mg/kg/day after 90 days of daily dosing (1.0 and 0.6 x therapeutic dosing regimen, respectively, based on a 14-day cumulative AUC). Although vacuolar degeneration (vacuolization) was seen at all dose levels in rat, also in recovery animals, the applicants proposed NOAEL levels in rat (10 mg/kg/day after 28 days, and 5 mg/kg/day after 90 days, equal to 0.7 and 0.6 x therapeutic dosing regimen, respectively, based on a 14-day cumulative AUC) is also considered to be acceptable based on the mild effects seen.

Tissue distribution and toxicity

The toxicity of dalbavancin correlated with its tissue distribution. Dalbavancin and its metabolites are cationic amphiphilic molecules. Lipophilic amine molecules like dalbavancin distribute into tissues primarily by highly favourable and nonsaturating partition and subsequently bind to the phospholipid components of membranes and concentrations of dalbavancin in tissue correlate with tissue concentrations of acidic phospholipids (highest concentrations in kidney >liver >lung >spleen >thymus). In studies with radiolabeled dalbavancin in dogs about 14% of the dose was recovered in the liver 70 days post dose while only about 0.2% of the dose was recovered in the liver at 70 days post dose in a similar study in rat. Dalbavancin thus seem to be present in higher concentrations, for longer periods of time, in dog liver compared to rat liver. This higher hepatic concentration in dogs may explain the observation that morphologic hepatic effects were primarily seen in dogs, while the predominant effect in rats was transaminase elevations.

Genotoxicity

Dalbavancin was evaluated in a battery of genotoxicity assays including a bacterial reverse mutation assay, *in vitro* mammalian cell assays for gene mutation and chromosomal damage and an *in vivo* mouse micronucleus assay. Dalbavancin was concluded not to have any genotoxic potential.

Exposure levels *in vivo* and in particular exposure to bone marrow have been discussed by the applicant during the procedure. CHMP agreed that metabolism and formation of metabolites were expected to be similar in mouse as in other species (despite this was not studied) and that extrapolation of exposure data obtained in mice indicated that an acceptable exposure to dalbavancin and its metabolites was achieved in the *in vivo* micronucleus assay.

Carcinogenicity

No carcinogenicity studies have been conducted. This is considered acceptable based on the short clinical dosage regimen (2 doses separated by 1 week and expected treatment not more than once a year) and based on the negative results from the genotoxicity assays performed with dalbavancin.

Reproduction and Developmental Toxicity

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).

In rats, the paternal and maternal NOELs, as well as NOELs for mating and fertility and embryo foetal development, were 15 mg/kg/day (~1-1.5x therapeutic dosing regimen, based on a 14-day cumulative AUC). The NOEL for viability and growth in offspring was 30 mg/kg/day. At 45 mg/kg/day in rats (~3 x therapeutic dosing regimen, based on a 14-day cumulative AUC) there was reduced fertility and an increased incidence of embryo lethality, reductions in foetal weight and skeletal ossification and increased neonatal mortality. The reduced fertility at 45 mg/kg/day is concluded to be secondary to the renal impairment based on published studies in rats with surgically induced renal impairment and stable uraemia. A similar conclusion was made during the assessment of the previous submission.

In rabbits, the maternal NOEL was 5 mg/kg/day. The highest dose tested, 15 mg/kg/day, was the developmental NOEL, but abortion occurred at this dose in conjunction with maternal toxicity. The 14- day cumulative AUC in the rabbit developmental and reproduction toxicity study (15 mg/kg/day dose) is estimated to be approximately equal to the cumulative AUC for the therapeutic dosing regimen in human (based on extrapolation of the AUC determined in the single dose rabbit PK study).

No evidence of a teratogenic effect was found.

In the pre-/postnatal development study reproduction toxicity (reduced pup survival) as well as dystocia and prolonged gestation were observed in association with maternal toxicity in the high dose group (30 mg/kg). No adverse findings related to dalbavancin were observed in surviving rats of the F1 generation. Dalbavancin was found to cross the placenta and to be excreted in milk of rats.

The toxicity profile observed in juvenile rats is consistent with that previously observed in adult rats at the same dose levels.

Local Tolerance

Dalbavancin is considered to be a non-irritant for the skin and eye, as well as after intravenous injection. Perivenous injection of dalbavancin gave edema and erythema.

Other toxicity studies

Immunotoxicity

Dalbavancin did not have any skin sensitizing capacity in the Guinea-pig maximization test.

A decrease in humoral immune response and NK cell numbers were seen at 40 mg/kg/day but since no functional effects on innate immunity or activity was seen, the decreases seen is not considered clinically relevant. In addition no effect on cell mediated immunity was seen.

The lymphoid depletion or necrosis observed in spleen, lymph nodes and thymus of dogs treated at doses of ≥10 mg/kg/day for at least 4 weeks were considered secondary to other manifestations of systemic toxicity and are not considered to indicate a specific immunotoxic effect of dalbavancin. Similar changes were not observed in rats.

Phototoxicity

The molar extinction coefficient at the maximum absorption at 284 nm is below 1000 L/M/cm, and dalbavancin do not have any significant absorption within the range 290 – 700 nm. The absence of phototoxicity testing is therefore considered to be acceptable.

2.3.5. Ecotoxicity / environmental risk assessment

Dalbavancin $PEC_{SURFACEWATER}$ value is indicated to be below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Dalbavancin is thus not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

In vitro screening of 120 receptors, ion channels, transporters and enzymes , revealed several targets with IC_{50} values that were below the plasma Cmax levels obtained in clinical studies (C_{max} = ~250-300 µg/mL (165 µM)). However, an overview of data on expression, physiological function, and known agonists/antagonists, for the secondary pharmacological targets where an IC_{50} level less than 2-fold the human unbound Cmax for dalbavancin revealed no specific concerns. In addition a review of the phase 2/3 integrated safety database has not revealed any specific drug-drug interactions in dalbavancin-treated subjects, or a safety profile different from the comparators.

Non-clinical safety pharmacology studies on cardiovascular, respiratory, CNS and autonomic nervous systems were also concluded not to indicate any effects, except effects on blood pressure and small increase in heart rate which were associated with hives, skin swelling and erythema, indicating a possible involvement of histamine release. ("Infusion-related reactions" is included as a warning in section 4.4 of the SmPC.) Plasma exposure at single dose administrations used in e.g. studies on respiratory, CNS and autonomic nervous systems is expected to have been substantially lower than the expected human clinical exposure. However, based on the available clinical safety data this is not considered to be critical.

Clearance and volume of distribution of dalbavancin scale allometrically by species body weight and concentrations and exposures were dose proportional within species and long residence times were observed in all species investigated. Volume of distribution was approximately 0.2 L/kg (similar to the extracellular water volume) indicating an interstitial distribution of dalbavancin. Dalbavancin was widely distributed throughout the body and was slowly cleared from all of the 40 tested tissues and organs in rats. Tissue concentrations in some tissues (e.g. adrenals, spleen and lymph nodes) seemed to have a longer half-life compared to plasma. Considering the administration of only two doses to humans, one week apart, possible accumulation and related histopathological changes seen in repeat dose toxicology studies are not likely to be of relevance for the human situation. Dalbavancin was shown to be stable in vitro in incubations with rat, dog, and human liver microsomes, as well as in presence of rat, dog, and human hepatocytes. OH-dalbavancin which was found in in vivo studies was not observed in liver microsomal or hepatocyte incubates. The biotransformation pathways of dalbavancin to its major metabolites, OH-dalbavancin and MAG have not been elucidated. MAG is also an impurity and present in the drug substance and drug product and it is thus not known if MAG is a "true" metabolite or not. However, based on the higher total amount of MAG in excreta as compared to the total amount administered via the batches used in studies in dog and rat MAG is concluded to be formed in vivo via secondary biotransformation and/or chemical modification/degradation.

In repeat dose toxicology studies (up to 3 month exposure) dalbavancin was shown to induce similar systemic toxicity in both rats and dogs with the main target organs being kidneys, liver and the haematological system. "Nephrotoxicity" and "Hepatic disorders" are included as "Important potential risks" in the RMP. Haematological undesirable effects (anemia, thrombocytosis, eosinophilia, leucopenia, neutropenia) are included as "uncommon adverse reactions" in the SmPC (Section 4.8) and are included as "important identified risks" in the RMP. In addition, vacuoles and/or dark pigment were observed in the cytoplasm of parenchymal cells in a variety of tissues, but since there was no correlation to cellular damage or organ dysfunction and the presence of pigment vacuoles and/or dark pigment is interpreted as evidence of increased cell membrane turnover and accumulation of lipofuscin and not considered to be adverse. The applicant concluded that these changes were attributed to tissue phospholipidosis, but no data to support this conclusion were presented.

Vacuolization and cellular apoptosis were identified in the acinar pancreas of rats and the possible effect on endocrine pancreas and glucose homeostasis was addressed during the previous submission and were also

discussed by the applicant. The vacuolization of acinar pancreas was not considered to be of relevance for a possible effect on glucose homeostasis, as also concluded previously. In addition, based on the mild and reversible effects seen in the rat, the small and variable differences in GI-effects seen between dalbavancin and comparator treated patients in the clinic, and the limited duration of clinical administration of dalbavancin the effects on the acinar pancreas seen in the rat were concluded to likely be of less clinical importance. Dalbavancin is concluded not to be genotoxic based on results from bacterial and mammalian cell assays for gene mutation and chromosomal damage and an in vivo mouse micronucleus assay. No carcinogenicity study has been performed which was considered acceptable by the CHMP based on the short clinical dosage regimen and the negative results obtained in the genotoxicity studies performed.

In the reproductive and developmental toxicity studies a reduced fertility and an increased incidence of embryo lethality, reductions in foetal weight and skeletal ossification and increased neonatal mortality were seen. In addition abortion occurred at doses inducing maternal toxicity in rabbits. No evidence of a teratogenic effect was found in either rats or rabbits. Dalbavancin was found to cross the placenta and to be excreted in milk of rats. The toxicity profile observed in juvenile rats was consistent with that previously observed in adult rats at the same dose levels. The reduced fertility at 45 mg/kg/day was concluded to be secondary to the renal impairment based on published studies in rats with surgically induced renal impairment and stable uraemia.

Local tolerance, immunotoxicity and phototoxicity have also been addressed and no issues have been identified. Dalbavancin drug substance and its corresponding drug product contain several impurities which have been toxicologically qualified and/or are specified at acceptable levels. Dalbavancin is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical part of the dossier is considered to be sufficient. No objection or concern was raised by the CHMP at the non-clinical level.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK Safety	VER001-1	To establish safety & maximum tolerated dose. To establish PK of single & multiple doses. To establish dose-limiting toxicities	Phase 1, randomized dose escalation Placebo controlled	Dalbavancin: 70, 140, 220, 360 mg Multiple-dose IV dalbavancin: qd for 7 days: starting dose 70 mg. Single or multiple dose IV placebo	23 total 11 6 6	Healthy subjects, 18–60 years	Single dose 7 days Single dose or 7 days

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK Safety	VER001-2	To establish safety, dose limiting toxicities & maximum tolerated dose. To characterize PK. To assess serum bactericidal activity at trough & extent of tissue penetration	Phase 1, randomized dose escalation	Single dose IV dalbavancin: 140, 220, 350, 500, 630, 840, 1120 mg Multiple dose IV dalbavancin for 7 days. 300 mg on Day 1 given as 150 mg q12h followed by 30 mg/day for 6 days Dose escalation proceeds as follows: 400/40 mg, 600/60 mg, 800/80 mg, 1000/100 mg. Single or multiple dose IV placebo	52 total 21 18 13	Healthy subjects, 18–55 years	Single dose 7 days Single dose or 7 days
PK Safety Special population	VER001-3	To assess the pharmacokinetics of dalbavancin administered intravenously in subjects with mild to moderate renal impairment.	Phase 1, randomized double blind Placebo controlled	Single dose IV dalbavancin: 70 mg Single dose IV placebo	5 total 3 2	Subjects with mild or moderate renal impairment, 18-75 years	Single dose Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety Efficacy PK/PD	VER001-4	To evaluate safety & efficacy (clinical & microbiological) relative to standard of care treatment, vancomycin. To obtain PK and PD data.	Phase 2, randomized, open-label vs. vancomycin	Grp A: Weekly IV dalbavancin: 1000 mg on Day 1, 500 mg on Day 8. Grp B: Daily IV dalbavancin: 650 mg on Day 1, 65 mg on Days 2–14 (this arm was discontinued). Grp C: 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.	74 total 33 8 34	Subjects ≥18 years with signs of bacteremia associated with a suspected or known diagnosis of catheter-related blood stream infection	14 days for subjects with *S. aureus* infection, and 7 to 14 days for all other pathogens

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety Efficacy	VER001-5	To evaluate efficacy (clinical & microbiological), safety, tolerability of 2 dose regimens of dalbavancin relative to standard therapy. To explore PD information on clinical response rates relative to dalbavancin plasma concentration data.	Phase 2, randomized, open label Physician designated comparator study	IV dalbavancin: 1100 mg (single dose) on Day 1 IV dalbavancin: 1000 mg on Day 1, 500 mg on Day 8. Standard antiobiotic therapy: as defined by investigator prior to randomization	62 in total Study Arm 1 20 Study Arm 2 21 Study Arm 3 21	Subjects ≥18 years with SSTI with suspected or confirmed Gram-positive bacterial pathogens, involving deeper soft tissue and or requiring significant surgical intervention.	Single dose (7 days) Multiple dose (14 days) In accordance with labeling instructions
Safety Efficacy	VER001-8	To compare the clinical efficacy and safety of dalbavancin in the treatment of adults with uncomplicated SSTI relative to a standard care of treatment, cefazolin possibly followed by cephalexin. To compare the microbiological efficacy between treatment arms	Phase 3, randomized double blind vs cefazolin	Dalbavancin: 1000 mg on Day 1, with the option to follow 500 mg on Day 8, possible switch to oral placebo q6h. Group B: IV cefazolin: 500 mg q8h, possible switch to oral cephalexin 500 mg q6h.	553 in total 367 186	Adults >18 years old with uncomplicated SSTI suspected to be caused by Gram-positive bacterial pathogens and expected to require at least 24 hours of parenteral therapy	7–14 days (IV plus oral)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety Efficacy	VER001-9	To compare clinical efficacy and safety of dalbavancin with that of linezolid in adults with cSSTI due to Gram-positive pathogens. To compare the microbiological efficacy between treatments and to obtain dalbavancin PK/PD data.	Phase 3, randomized, double blind study	IV dalbavancin: 1000 mg on Day 1, 500 mg on Day 8, possible switch to oral placebo q12h IV linezolid: 600 mg q12h, possible switch to oral linezolid 600 mg q12h	873 in total 583 290	Adults >18 years old with complicated SSTI due to Gram-positive pathogens, with at least one systemic sign of infection	14 days
PK Safety ADME	VER001-10	To determine concentrations of dalbavancin in skin tissues. To calculate the extent of renal excretion of dalbavancin	Phase 1, open label, no control	Single dose IV dalbavancin: 1000 mg	6	Healthy subjects 18–65 years, normal baseline audiology assessment.	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK Safety Special population	VER001-11	To study the safety, tolerability, and PK of dalbavancin in subjects with severe renal impairment or end stage renal disease (ESRD) compared with age, gender and weight matched healthy subjects with normal renal function	Phase 1, open label, no control	Single dose IV dalbavancin 500 or 1000 mg Group A1: 500 mg Group A2: 1000 mg Group B1: 500 mg prior to dialysis Group B2: 500 mg after dialysis Group C: 500 mg	22 in total Group A: Severe renal impairment: 6 4 Group B: ESRD: 3 3 Group C: Healthy: 6	Severe renal impairment or ESRD, or healthy subjects, ≥18 to <80 years	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK Safety Special population	VER001-12	To study the safety tolerability, and PK of dalbavancin in subjects with mild, moderate and severe hepatic impairment compared with age, gender, and weight-matched healthy subjects with normal hepatic function. If necessary to recommend a dose adjustment for subjects with hepatic impairment.	Phase 1, open label	IV dalbavancin 1000 mg on Day 1 and IV dalbavancin 500 mg on Day 8	27 in total Group A: Mild hepatic impairment: 6 Group B: Moderate hepatic impairment: 6 Group C: Severe hepatic impairment: 5 Group D: Healthy: 10	Mild, moderate or severe hepatic impairment or healthy subjects, ≥18 to ≤80 years.	Two doses in 8 days

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK Safety Special population	VER001-13	To study the safety, tolerability and PK of dalbavancin in subjects with mild and moderate renal impairment compared to age, gender, and weight matched healthy subjects with normal renal function.	Phase 1, open label no control	Single dose IV dalbavancin: 1000 mg	21 in total Group A: Healthy Subjects: 9 Group B: Mild renal impairment: 6 Group C: Moderate renal impairment: 6	Subjects ≥18 to <80 years with varying degrees of renal function	Single dose
Safety PD	VER001-15	To assess the effect of intravenous dalbavancin on the intestinal flora of healthy subjects	Phase 1, open label, no control	Single IV dose dalbavancin: 1000 mg	12	Healthy subjects 18-40 years	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety Efficacy	VER001-16	To evaluate the clinical and microbiological efficacy, safety and tolerability of dalbavancin in the treatment of adults with SSTI known or suspected to be due to MRSA compared with vancomycin.	Phase 3 open label, randomized study with comparator vancomycin	IV dalbavancin: 1000 mg on Day1, 500 mg on Day 8. IV vancomycin: 1000 mg q12h; after 24 hours parenteral therapy possible switch to oral cephalexin 500 mg 1 g q8h if pathogen was susceptible	156 total 107 49	Patients ≥18 years of ages with SSTI, complicated or uncomplicated with infection suspected or confirmed due to MRSA.	14 days duration for cSSTI, 7 days or 14 days for uSSTI.
PK Safety ADME	VER001-19	To study the excretion of dalbavancin in healthy subjects	Phase 1, open label, no control	Single IV dose dalbavancin: 1000 mg	9	Healthy subjects 19–65 years	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety PK	A8841004	To investigate the pharmacokinetics, safety and tolerability of dalbavancin in hospitalized adolescents, aged 12 through 17 years receiving standard intravenous anti-infective treatment for bacterial infections	Phase 1, open label	Dalbavancin 1000 mg IV Dalbavancin 15 mg/kg	10 total 5 5	Hospitalized adolescents, aged 12–17 years receiving standard intravenous anti-infective treatment for bacterial infections	Single dose
Safety PK	DUR001-101	Pilot study to determine plasma concentrations following administration of IV dalbavancin	Phase 1, single-dose, one-period, open-label study	IV dalbavancin 1500 mg	8	Healthy subjects 18–55 years	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety PK Effect on QT/QTc	DUR001-102	To study the electrocardiographic effects of dalbavancin in healthy male and female subjects	Phase 1, randomized, placebo- and positive-controlled parallel group	IV dalbavancin 1500 mg IV dalbavancin 1000 mg moxifloxacin 400 mg PO Placebo IV	200 total 50 50 50 50	Healthy male and female subjects 18–55 years	Single dose
Safety PK	DUR001-103	Evaluation of pharmacokinetics, safety and tolerability of a single 1000 mg intravenous dose of dalbavancin in healthy Japanese subjects	Phase 1, double blind, placebo controlled	IV dalbavancin 1000 mg IV dalbavancin 500 mg Placebo IV	18 total 10 5 3	Healthy Japanese subjects 18–55 years	Single dose

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety PK	DUR001-104	To evaluate the safety, tolerability, and pharmacokinetics of IV dalbavancin administered weekly for 4 to 8 weeks to healthy adult subjects.	Open-label, multiple-dose, parallel cohort, safety, tolerability, and pharmacokinetic study of increasing dosing durations.	Dalbavancin 1000 mg Week 1, 500 mg Weeks 2–4 1000 mg Week 1, 500 mg Weeks 2–6 1000 mg Week 1, 500 mg Weeks 2–8	18 total 6 6 6	Healthy subjects 18–55 years	4 weeks 6 weeks 8 weeks
Safety Efficacy	DUR001-301	To compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin and linezolid) for the treatment of acute bacterial skin and skin structure infections	Phase 3, randomized, double-blind, double-dummy	**IV dalbavancin**: 1000 mg, or dose-adjusted for Cr_{Cl} on Day 1, 500 mg, or dose-adjusted for Cr_{Cl} on Day 8 **IV vancomycin**: 1000 mg q12h, or dose-adjusted for renal impairment for 14 days; possible switch to oral therapy after 3 days to linezolid 600 mg q12h.	573 total 288 285	Adults aged 18–85 with abSSSI known or suspected to be caused by gram-positive bacteria	Multiple dose (10–14 days)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	
Safety Efficacy	DUR001-302	To compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin and linezolid) for the treatment of acute bacterial skin and skin structure infections	Phase 3, randomized, double-blind, double-dummy	**IV dalbavancin**: 1000 mg, or dose-adjusted for Cr_{Cl} on Day 1, 500 mg, or dose-adjusted for Cr_{Cl} on Day 8 **IV vancomycin**: 1000 mg q12h, or dose-adjusted for renal impairment for 14 days; possible switch to oral therapy after 3 days to linezolid 600 mg q12h.	739 total 371 368	Adults aged 18–85 with abSSSI known or suspected to be caused by gram-positive bacteria	Multiple dose (10–14 days)	
Abbreviations: abSSSI = acute bacterial skin and skin structure infections; ADME = absorption,distribution,metabolism,excretion; Cr_{Cl} = creatinine clearance; CSR = Clinical Study Report; cSSTI = complicated skin and soft tissue infections; ESRD = end stage renal disease; grp = group; IV = intravenous; MRSA = methicillin-resistant *S. aureus*; N/A = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; PO = per os; q12h = every 12 hours; q4h = every 4 hours; q6h = every 6 hours; q8h = every 8 hours; qd = once daily; SSTI = skin and soft tissue infections; uSSTI = uncomplicated skin and soft tissue infections								

2.4.2. Pharmacokinetics

Absorption

The administration of dalbavancin is intravenous.

Distribution

As already mentioned, dalbavancin is administered intravenously and its pharmacokinetics was best described by a three-compartment model: an initial distributive phase characterized by a $t_{1/2}$ of ~2.5 h, a beta phase accounting for the majority of drug elimination with a $t_{1/2}$ of ~5 days, and a terminal $t_{½}$ of approximately 16 days (range 14 days to 17 days) (see below figure). The plasma protein binding, investigated over a concentration range covering the therapeutic concentrations of dalbavancin, was on average 93% and does not differ between subjects with normal renal and hepatic function, and subjects with severe renal or hepatic impairment. The protein binding of MAG (a component of the drug substance) and OH-dalbavancin (metabolite found in urine and plasma) was determined to 87% and 72%, respectively. These compounds display *in vitro*

activity, but only OH-dalbavancin has been detected in plasma and at concentrations close to the lower limit of quantification.

Figure 1 Mean dalbavancin plasma concentration versus time on a linear scale with sd.

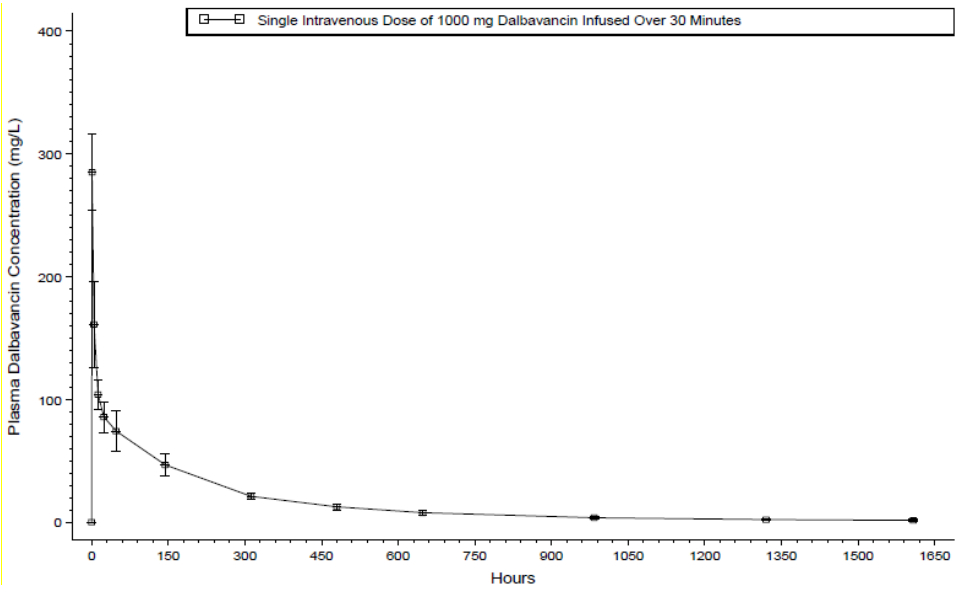


Table 1 Pharmacokinetic parameters of dalbavancin in plasma after single iv dose (1000 mg)

	Mean	SD	CV%	Min	Max
Dalbavancin in Plasma					
C_{max} (mg/L)	285	31.1	10.9	244	336
$AUC_{(0\text{-}144)}$ (mg.h/L)	10806	1926	18	8688	14982
$AUC_{(0\text{-}t)}$ (mg.h/L)	24248	3511	14	20100	32035
$AUC_{(0\text{-}inf)}$ (mg.h/L)	25088	3685	15	20679	33132
CL (L/h)	0.0405	0.0053	13.1	0.0302	0.0484
V_{ss} (L)	13.8	2.3	16.5	9.8	17.3
$t_{1/2}$ (h)	372	28	7	333	405

Dalbavancin single-dose pharmacokinetics appeared to be linear in the range 140-1120 mg, as were maintenance regimens ranging from 300/30 to 1000/100 mg, and there was no indication of time-dependent kinetics.

Metabolism and elimination

There are no mass balance data for dalbavancin in human subjects. Following single dosing of dalbavancin, ~30% of the dose was recovered in urine as unchanged drug and ~20% of the dose in faeces. Results from two renal impairment studies and from the population pharmacokinetic (PPK) analysis suggested that the CL associated with renal function accounts for approximately 30% of the total CL for an individual with a normal renal function.

One metabolite, OH-dalbavancin, was detected in urine (8-12% of the dose) and at low levels in plasma. Mannosyl aglycone (MAG), a component of the drug substance and a degradation product, was also detected in small amounts in urine. This compound had a faster clearance into urine than dalbavancin, which suggests that MAG is not formed *in vivo* from dalbavancin. The data presented on faecal recovery, OH-dalbavancin present in urine, and the estimated ~30% contribution of non-renal elimination to the total CL, suggest that the liver

contributes to the elimination of dalbavancin. Dalbavancin was metabolically stable in *in vitro* assays (hepatocytes, liver and kidney microsomes).

Dose proportionality and time dependencies

- **Dose proportionality**

Dose linearity was evaluated from pharmacokinetic data in study VER001-2, a phase 1, randomized, double-blind, placebo-controlled, single- and multiple dose escalation study designed to assess the safety and pharmacokinetics and pharmacodynamics of dalbavancin administered intravenously over 30 minutes to normal, healthy subjects. Fasting was not required and there were no dietary restrictions or requirements.

Fifty-two subjects were randomized to double-blind treatment with dalbavancin (39) or placebo (13). Fifty-one subjects completed the study and one subject (dalbavancin multiple-dose) prematurely discontinued at the request of the subject. In the single dose evaluation doses ranged from 140 mg to 1120 mg. In the multiple-dose phase of the study, dosing consisted of a loading dose (LD), administered as two equal doses given 12 hours apart (q12h), followed by a once daily (qd) maintenance dose (MD) and ranged from 300/30mg to 1000/100 mg.

Linear regression analyses were conducted for the individual C_{max} and AUC values versus dose. Both analyses showed a linear relationship between C_{max}/AUC and dose.

- **Time dependency**

Time dependency was evaluated in study VER001-1, a randomized, placebo-controlled, single- and multiple-dose, dose escalation study in healthy volunteers. Subjects in the single dose group were administered a single dose of dalbavancin via IV infusion at a starting dose of 70 mg on Day 1. Subjects in the multiple-dose group received dalbavancin once daily for 7 days via IV infusion at a starting dose of 70 mg. Dose escalation for both single and multiple-dose groups proceeded to 140, 220, 360, 560, and 900 mg and all subjects were observed for 28 days.

The $t_{1/2}$ of dalbavancin following a single dose ranged from 166 to 212 hours. Following multiple IV infusion doses of 70 mg dalbavancin once daily for 7 days, significant accumulation occurred. The 24-hour trough values following multiple-dose administration of 70 mg showed an approximate 5-fold increase from Day 1 to Day 7, 6.8 mg/L and 32.5 mg/L, respectively. The mean Cmax value on Day 7 after multiple doses of dalbavancin was 48.5 mg/L and the mean $t_{1/2}$ following the last dose was 194 hours, similar to that observed following single doses. The CHMP agreed that there was no indication of time-dependent kinetics. Furthermore, as dalbavancin is intended as a two-dose regimen, a time-dependence in kinetics would unlikely be clinically significant.

Special populations

The effect of renal impairment was investigated in studies specifically targeting a population with renal impairment (mild, moderate, severe and ESRD) as well as in the PPK analysis. In subjects with moderate renal impairment, there was a 50% increase in dalbavancin AUC_{inf} and the CL was 35% slower compared to subjects with normal renal function. AUC_{inf} of dalbavancin increased approximately 2-fold in subjects with severe renal impairment, and mean CL was reduced by ~50%. In patients with severe renal impairment (CLcr <30 ml/min), the dose of dalbavancin will be reduced. The dosage regimen was based on simulations performed with the PPK model, qualified against the data obtained in subjects with renal impairment. The dose adjustment aimed at

minimizing the overall exposure of drug (AUC_{inf}), while maintaining concentrations above the same levels observed for subjects with normal renal function throughout the 14-day treatment interval.

Subjects with ESRD receiving haemodialysis had a less marked increase in AUC_{inf} compared to subjects with severe renal impairment. It is not fully understood why the plasma exposure to dalbavancin seemed to be less affected in these patients. Dalbavancin was not detected in the dialysate samples, but dalbavancin may have been present in the dialysate at concentrations below the lower limit of quantification. The increased exposure to dalbavancin in subjects with severe renal impairment could also in part be driven by changes in non-renal clearance (changes in activity of enzymes and transporters) secondary to accumulation of uremic toxins. This effect may be less pronounced in patients with ESRD undergoing haemodialysis, due to the beneficial effects of haemodialysis. The conclusion not to dose adjust dalbavancin in subjects who are on regular haemodialysis was nevertheless based on a small number of subjects.

The study in patients with hepatic impairment suggested that patients with a moderate to severe impairment had a ~30% lower exposure compared to healthy subjects. The cause and the clinical significance of the decreased exposure in subjects with moderate and severe hepatic function are unknown, which is addressed in the Xydalba SmPC. Use of dalbavancin in patients with moderate and severe hepatic impairment is also included in the RMP as missing information.

In addition to the effect of reduced renal and hepatic function, a number of covariates were identified as statistically significant, but not clinically relevant, predictors of dalbavancin exposure in the population pharmacokinetic analysis (gender, age, BSA and albumin). Race was examined as a possible covariate, but did not have any statistically significant effects on the pharmacokinetic model and the pharmacokinetics of dalbavancin seemed to be similar in healthy Japanese subjects as compared to North American/European subjects.

The pharmacokinetics of dalbavancin in subjects aged 12 to 16 years were investigated in a clinical study. Overall exposure and C_{max} appeared to be slightly lower than that observed in adults. Apparent terminal $t_{½}$ was relatively consistent with what was seen in adults.

Pharmacokinetic interaction studies

Dalbavancin is not metabolised by CYP450 enzymes in vitro, therefore co-administered P450 inducers or inhibitors are unlikely to influence the pharmacokinetics of dalbavancin. The CHMP requested the applicant to perform *in vitro* experiments investigating dalbavancin as a substrate of OATP1B1, OATP1B3, BCRP and P-glycoprotein as post-authorisation measures.

The interaction potential of dalbavancin on medicinal products metabolised by CYP450 enzymes is expected to be low since the compound did not inhibit or induce CYP450 enzymes in vitro. It is not known if dalbavancin is an inhibitor of transporters. The CHMP requested the applicant to also address this post-approval.

2.4.3. Pharmacodynamics

Mechanism of action

Dalbavancin is a semi-synthetic glycopeptide antibiotic, structurally related to teicoplanin. Like other glycopeptide antibiotics, dalbavancin interferes with cell wall formation by binding to the D-alanyl-D-alanine (D-ala-D-ala) terminus of the peptidoglycan, preventing cross-linking. Dalbavancin is active against most relevant groups of Gram-positive bacteria for cSSTI, including strains of methicillin-resistant *Staphylococcus*

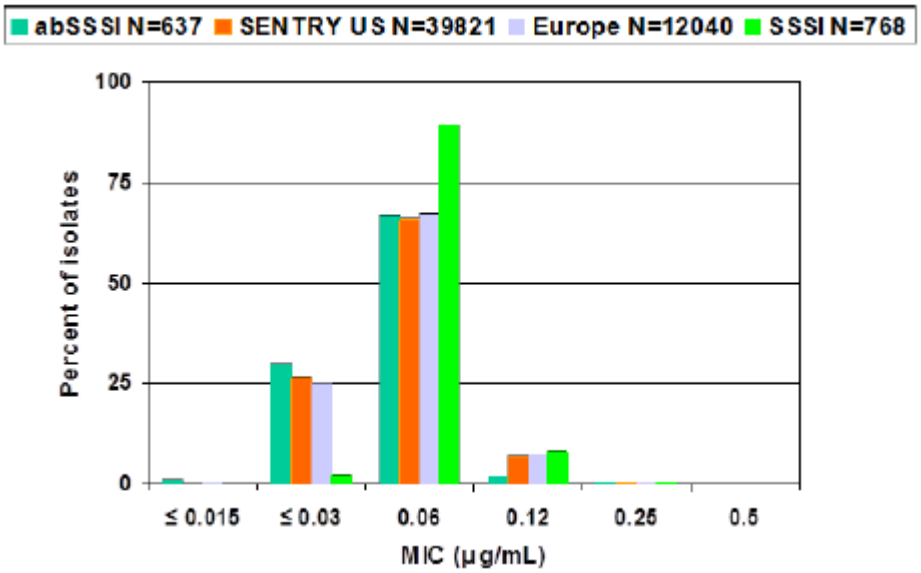
aureus (MRSA). Compared with typical glycopeptides, dalbavancin is said to be active against VanB and VanC enterococci and to possess enhanced activity against staphylococci, particularly coagulase-negative staphylococci (CoNS) and some *S. aureus* with reduced susceptibility to glycopeptides (GISA).

The mechanism of action is bacteria-specific, and there were no data from the safety pharmacology and toxicology studies and clinical trials which indicated any secondary pharmacodynamic effects.

Primary and secondary pharmacology

The *in vitro* antibacterial activity of dalbavancin was tested on more than 70.000 clinical isolates of Gram-positive bacteria worldwide collected from 2007-2012. The activity was also studied in several animal models of infection. The majority of isolates tested were staphylococci and streptococci. MIC ranges were narrow with MIC_{90} values generally below or at 0.06 mg/L for staphylococci and streptococci.

Figure 2 Dalbavancin MIC Distribution: MRSA from Clinical Trial (cSSTI and SSTI Baseline Isolates) and Surveillance Studies



Source: ISM Table 4.1; R. Jones, JMI Laboratories, SENTRY database; Deane 2012; Jones 2011a; IHMA Database; ABSSSI studies are DUR001-301 and DUR001-302

The susceptibility studies demonstrated that the *in vitro* potency of dalbavancin was in almost all cases equal to or greater than comparators, including vancomycin, teicoplanin and linezolid.

Table 2 Comparative Activity of Dalbavancin against 39,824 Isolates of S. aureus from the US (2002–2012)

Antimicrobial Agent	MIC (µg/mL)			%S /%I / %R[a]	
	50%	90%	Range	CLSI	EUCAST
Dalbavancin	0.06	0.06	≤0.03–0.5	- / - / -	- / - / -
Vancomycin	1	1	≤0.12–4	>99.9 / <0.1 / 0.0	>99.9 / 0.0 / <0.1
Teicoplanin	≤2	≤2	≤2–8	100.0 / 0.0 / 0.0	99.7 / 0.0 / 0.3
Oxacillin	>2	>2	≤0.25– >2	47.5 / 0.0 / 52.5	47.5 / 0.0 / 52.5
Erythromycin	>2	>2	≤0.2– >2	35.9 / 0.9 / 63.2	36.1 / 0.4 / 63.5
Clindamycin	≤0.25	>2	≤0.25– >2	76.5 / 0.2 / 23.3	76.1 / 0.4 / 23.5
Daptomycin	0.25	0.5	≤0.12–4	99.9 / - / -	99.9 / 0.0 / 0.1
Levofloxacin	≤0.5	>4	≤0.5– >4	56.6 / 1.1 / 42.3	56.6 / 1.1 / 42.3
Linezolid	1	2	≤0.25– >8	>99.9 / 0.0 / <0.1	>99.9 / 0.0 / <0.1
Tetracycline	≤4	≤4	≤4– >8	95.1 / 0.5 / 4.4	89.7 / 0.4 / 9.9

[a] Criteria as published by CLSI 2013 and EUCAST (2013)

Data from R. Jones, JMI Laboratories, SENTRY database.

However, the activity against enterococci are more variable with MIC ranging up to >4 mg/L for vancomycin resistant isolates, generally due to the presence of the vanA determinant.

Data from Europe for key pathogens are consistent with the US susceptibility patterns, MIC_{90} values for Gram-positive aerobic cocci do not exceed 0.12 mg/L, except for vancomycin-resistant enterococci.

Table 3 Dalbavancin Susceptibility of Key Pathogens Collected in European Hospitals from 2006 to 2009.

Organism (N)	No. Occurrences at Dalbavancin MIC (µg/mL)					MIC	
	≤0.03	0.06	0.12	0.25	≥0.5	50%	90%
S. aureus (11,658)	2,773	7,987	863	35	0	0.06	0.06
MRSA (3,183)	914	2,018	238	13	0	0.06	0.06
MSSA (8,475)	1,859	5,969	625	22	0	0.06	0.06
β-hemolytic streptococci							
All (1,997)	1,893	85	15	4	0	≤0.03	≤0.03
S. pyogenes (793)	781	10	1	1	0	≤0.03	≤0.03
S. agalactiae (817)	740	61	12	3	0	≤0.03	≤0.03
Viridans streptococci (845)	744	95	6	0	0	≤0.03	0.06
Enterococcus spp.							
Van-S (4,457)	1,412	2,301	655	80	9	0.06	0.12
Van-R (525)	18	58	38	10	401	4	>4

Data from Jones 2011a

Resistance to dalbavancin among Gram-positive bacteria appears to be limited to certain intrinsically glycopeptide-resistant species and to bacteria expressing the VanA phenotype. No emergence of resistance to dalbavancin was detected in animal infection experiments, or *in vitro* studies designed to detect development of resistance, or in the clinical studies.

Any efficacy benefits of dalbavancin compared to the older glycopeptides would heavily depend on clinical activity against isolates with reduced susceptibility to vancomycin and/or teicoplanin. Although higher activity of

dalbavancin based on *in vitro* data compared to other glycopeptides (vancomycin and teicoplanin) there seem to be a certain degree of cross-resistance within this class.

Table 4 Activity of Dalbavancin against Selected Clinical Isolates Including Challenge Organisms

Organism	N	MIC (µg/mL)		
		Range	50%	90%
S aureus (All)	319	0.015–16	0.06	0.12
MSSA	42	0.03–0.06	0.06	0.06
MRSA (non-MDR)	103	0.03–0.12	0.06	0.06
MRSA (MDR)	142	0.015–0.25	0.06	0.06
Linezolid-NS	5	0.03–0.06	NA	NA
hVISA	21	0.06–1	0.25	1
VISA	4	0.5–1	NA	NA
VRSA	2	2–16	NA	NA
CoNS (All)	301	≤0.008–2	0.06	0.12
MS	70	≤0.008–0.25	0.03	0.12
MR	220	≤0.008–0.5	0.06	0.12
hVICNS	6	0.5–1	NA	NA
VICNS	5	0.25–2	NA	NA

MSSA=Methicillin-susceptible *S. aureus*; MRSA=Methicillin-resistant *S. aureus*; MDR=multidrug-resistant; NS=non-susceptible; hVISA=Heterogeneous vancomycin-intermediate *S. aureus*; VISA=Vancomycin-intermediate *S. aureus*; CoNS=Coagulase-negative staphylococci; MS=Methicillin-susceptible; MR=Methicillin-resistant; hVICNS=Heterogeneous vancomycin-intermediate coagulase-negative staphylococci; VICNS=Vancomycin-intermediate coagulase-negative staphylococci;

The dalbavancin MIC range for phenotypically VanA (teicoplanin-resistant) enterococci is quite broad, with dalbavancin showing greater activity against some isolates.

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. Data from animal studies and human PK data as well as Phase 2 data indicate that dalbavancin should be dosed at less frequent intervals, which was the basis for dosage regimen (once a week) in the Phase 3 studies.

2.4.4. Discussion on clinical pharmacology

During the procedure, the validation of the bioanalytical methods was discussed and agreed by the CHMP after supplementary information provided by the applicant.

The applicant was requested to perform a number of post-authorisation measures, aiming at improving the understanding of potential drug-drug interactions with dalbavancin. *In vitro* investigations of dalbavancin as a substrate for hepatic uptake and efflux transporters will be performed, and the inhibitory potency against transport proteins will also be addressed.

Pharmacodynamics

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. 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. Teicoplanin-resistant vanB enterococci might be expected to also be resistant to dalbavancin. Additionally, dalbavancin has in general a somewhat reduced susceptibility against vancomycin-intermediate *S. aureus* (VISA) strains.

The maintenance of bactericidal levels of dalbavancin throughout the treatment period with proposed dalbavancin doses in humans, may contribute to a reduced potential for resistance emergence in pathogens at the site of infection. However, considering the slow elimination of dalbavancin and the fact that at least 20% is excreted unchanged in faeces, it seems that an ideal situation for emergence and/or selection of glycopeptide resistance would be created in the intestinal tract, with extensive periods of sub-inhibitory concentrations. The results from studies performed hitherto indicate however that there is possibly low probability of selection for glycopeptide resistance.

The susceptibility breakpoints determined by the EUCAST are 0.125 mg/L for both staphylococci and streptococci. Based on present clinical data, no pattern of decreased clinical success of decreased pathogen eradication associated with high MIC values could be identified. This may be due to the high eradication rate overall and the lack of isolates with high MIC values.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacokinetic program was considered acceptable by the CHMP. To further improve the understanding of the interaction potential of dalbavancin, the Applicant has been requested to perform two post-authorisation measures.

The clinical pharmacodynamic part of the file was considered sufficient by the CHMP. *In vitro* data, animal data and outcome of clinical studies imply that dalbavancin exerts potent activity against the major pathogens causing ABSSSI.

2.5. Clinical efficacy

The efficacy of dalbavancin for the targeted treatment indication was evaluated in 3 phase 3 studies (DUR001-301, DUR001-302, and VER001-9). Patients with infections consistent with ABSSSI were eligible for enrolment into the 3 pivotal studies. The CHMP was of the opinion that study VER001-9 was only to be considered as a supportive study for the current application. Additionally, 3 supportive studies (VER001-16, VER001-8, and VER001-5) evaluated the use of dalbavancin in SSTI subjects.

It should be noted that another marketing authorisation application was submitted in 2007 via the centralised procedure for dalbavancin and contained study VER001-9 as a single pivotal study. This application was withdrawn following the CHMP conclusion that the external validity of the study population of this trial was not convincingly demonstrated. The applicant now provides data from two new phase 3 studies, DUR001-301 and DUR001-302, in addition to the above mentioned study VER001-9 to support the current application.

2.5.1. Dose response studies

No formal dose finding program has been submitted. The rationale for the dosage regimen chosen (1000 mg on day 1 followed by 500 mg on day 8) for studies DUR001-301 and -302 are based on data from neutropenic murine thigh infection model, a Monte Carlo simulation on PK/PD data, as well as clinical data from a Phase 2 study (VER001-05) and the earlier performed Phase 3 study VER001-9

2.5.2. Main studies

Design and conduct of main clinical studies

Each of the pivotal phase 3 studies was randomized, double-blind (third party unblinded), multi-centre study. Patients with infections consistent with cSSTI, defined as infections involving deeper soft tissue or requiring significant surgical intervention, were eligible for enrolment. Studies DUR001-301 and DUR001-302 have similar design and were performed according to current EU guidelines.

The inclusion criteria for these more recently performed studies were patients with cSSTI such as major cutaneous abscess (in total < 30% of this type could be included), surgical site or traumatic wound infection, or cellulitis (the total affected area should involve at least 75 cm^2 of erythema, except if it involved the central face, then the area should be at least 50 cm^2), all characterised in line with existing FDA guidelines; and at least one clinical systemic sign of infection (elevated body temperature ≥38°C/100.4°F as measured by the patient/caregiver or investigator within 24 hours of baseline; white blood cell count >12,000 cells/mm^3; a manually performed white blood differential count with ≥10% band forms, regardless of peripheral white blood cell count), as well as infection severity such that a minimum of 3 days of IV therapy is appropriate for management of the cSSTI. According to the EMA scientific advice from 2010, the applicant was advised to aim for a considerable proportion of subjects meeting at least 2 SIRS criteria, as well as patients with co-morbidities such a diabetes mellitus, peripheral vascular disorders, concomitant bacteraemia, as these patients are more likely to have severe infection.

Patients with skin infections like superficial/simple cellulitis/erysipelas, impetiginous lesion, furuncle, or simple abscess that only required surgical drainage for cure were excluded. This was also the case for patients with infections that involved diabetic foot ulceration, a perirectal abscess or a decubitus ulcer. Exclusion of entities like diabetic foot infection and infected decubitus ulcer are considered acceptable as these are often associated with Gram-negative pathogens. The exclusion of diabetes foot, which would be considered a complicated infection, is also in line with the Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections EMA/CHMP/351889/2013). Diabetes foot infections are advised to be evaluated in separate dedicated studies.

Eligible subjects in studies DUR001-301 and DUR001-302 were randomized 1:1 to receive treatment with IV dalbavancin or IV vancomycin. Dalbavancin was administered as an initial 1000-mg dose, followed by a 500-mg dose on day 8. The dose of i.v. vancomycin was 1000 mg or 15 mg/kg (depending on the study site standard of care) q12h for 3 days (6 doses) to 14 days. Dosages were adjusted for renal insufficiency.

Seventy-two hours after study drug initiation, investigators had the option of switching subjects in the comparator regimen from IV vancomycin to oral linezolid 600 mg administered q12h provided that the criteria for a switch to oral therapy were met (i.e., in the previous 24 hours, the patient had 4 temperature measurements, each separated by approximately 6 hours, in which all 4 measurements were 37.6° C and unequivocal improvement in some or all of the clinical signs of the SSSI under study; if some signs had not improved, none should have worsened). The duration of treatment was 10 to 15 calendar days.

Systemic aztreonam could have been administered empirically at randomization for a presumed Gram-negative contribution to the cSSTI or to treat a culture-confirmed infection at any time during the study; empirical use of aztreonam post randomization was not permitted. Metronidazole (IV. or oral) could be used in both treatment groups for suspected anaerobic pathogens and *Clostridium difficile* infections.

The applicant has presented separate statistical analysis plans (SAP) for the two pivotal studies DUR001-301 and DUR001-302, as the US and European regulatory requirements are different regarding the primary efficacy endpoints. In accordance with the CHMP Guideline on the Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev 2), the EMA primary endpoint is the clinical response (i.e. success or failure) at the test-of-cure, as assessed by investigators, while the US regulators support an early efficacy endpoint at 48-72 hours after initiation of therapy comprised of presence/absence of fever and cessation of spread of erythema.

In the SAP presented to the EU regulators, the primary endpoint was the clinical response (success or failure) in the Clinically Evaluable (CE) patient population at the End-of Treatment (EOT) evaluation (study day 14-15). Dalbavancin was to be considered non-inferior to the comparator vancomycin/linezolid if the lower margin of the confidence interval for the difference in success rates between treatment groups was above 10%.

It is important to point out that all sample size and power calculations as well as the interim analyses for sample size re-calculation were based on the FDA primary endpoint in the ITT population, not the EMA primary endpoint in the CE-EOT population.

It should furthermore be noted that in several EMA guidelines, including the EMA 'Points to consider on switching between superiority and non-inferiority' (CPMP/EWP/842/99), the choice of analysis sets is described as follows: 'In a non-inferiority trial, the full analysis set and the PP analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation'. Whether non-inferiority has been proven should therefore be judged on both, the primary analysis on the CE-EOT analysis set and the results from the secondary efficacy analysis performed on the ITT analysis set.

CHMP noted that there were numerical differences in the success rates for the EMA primary endpoints at the time point of the interim analysis and in the final analysis. The applicant has provided additional clarification on these aspects. These were discussed by CHMP, which agreed that despite no clear explanations for the differences have been provided, these differences were not statistically significant and they were therefore judged not to affect the overall efficacy conclusions.

Table 5 Clinical success at EOT in patients randomized prior to and post interim analysis (CE-EOT and ITT populations)

	DUR001-301			DUR001-302		
	Dalbavancin	Vancomycin/ Linezolid	Difference (95% CI)	Dalbavancin	Vancomycin/ Linezolid	Difference (95% CI)
CE Population	246	243		324	302	
Clinical Success at EOT	214	222		303	280	
Randomized Prior to Interim Analysis	117 (88.0)	122 (93.1))	-5.1 (-13.1, 1.8)	140 (95.2)	114 (89.8)	5.4 (-1.0, 12.5)
Randomized Post Interim Analysis	97 (85.8)	100 (89.3)	-3.5 (-12.7, 4.9)	163 (92.1)	166 (94.9)	-2.8 (-8.3, 2.7)
ITT Population	288	285		371	368	
Clinical Success at EOT	236	247		329	315	
Randomized Prior to Interim Analysis	136 (81.0)	143 (86.1)	-5.1 (-13.6, 2.4)	151 (91.0)	136 (81.0)	10.0 (2.6, 17.6)
Randomized Post Interim Analysis	100 (83.3)	104 (87.4)	-4.1 (-12.7, 5.1)	178 (86.8)	179 (89.5)	-2.7 (-9.2, 3.8)

Differences were also noted between the study protocols of the two pivotal studies DUR001-301 and DUR001-302 regarding the criteria for inclusion into the CE-EOT populations. The applicant explained that these were needed based on the experience from the DUR001-301 study. CHMP agreed that the number of excluded patients by applying these criteria was small and was not considered to have significantly impacted the overall study results.

Study populations

In the 3 studies designed to evaluate the efficacy of dalbavancin in cSSTI, the following main patient populations were identified for the efficacy analyses, as follows:

Intent-to-treat (ITT) Population:

- Studies DUR001-301 and DUR001-302: All randomized patients regardless of whether or not they received study drug.
- Study VER001-9: All randomized patients who received at least 1 dose of study medication.

Safety Population (for studies DUR001-301 and 302):

- All patients in the ITT population who received at least 1 dose of dalbavancin or active comparator study drug. For Study VER001-9, the safety population was the same as the ITT population.

Microbiological Intent-to-treat (MicroITT) Population:

- All patients in the ITT population with at least 1 Gram-positive pathogen identified at baseline.

Clinically Evaluable (CE) Population:

- Patients with a cSSTI at baseline who did not violate the protocol in such a way that precluded clinical evaluability, according to specific protocol violation definitions. A CE population was identified for each visit, ie, end-of-therapy (EOT) visit and short-term follow-up (SFU) visit or test of cure (TOC; VER001-9 visit; 14 ± 2 days after completion of therapy); TOC in Studies DUR001-301 and DUR001-302 was equivalent to the EOT visit on Day 14.

Microbiologically Evaluable (ME) Population:

- Met all the criteria for the CE population and had a Gram-positive causative pathogen at baseline. An ME population was identified for each visit (EOT, SFU, TOC).

The CE population was the primary population for the analysis of clinical status at EOT. However according to the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, CPMP/EWP/558/95 rev 2, the CE and all treated populations should be viewed as co-primary, i.e. consistency in outcome between the CE and the ITT populations is considered crucial.

Clinical endpoints

Studies DUR001-301 and DUR001-302

Endpoints for assessment of clinical response were:

- Early clinical response (defined as cessation of spread and absence of fever) at 48-72 hours post-study drug initiation in the ITT population
- End-of-treatment (EOT) visit (Day 14-15) in the CE-EOT population.
- Short-term follow-up (SFU) visit (Day 28 ±2 days) in the CE-SFU population.
- Long-term follow-up (LFU) visit; targeted for Day 70, but the visit could have occurred from Day 60 through Day 88, in the CE-LFU population.

Primary Efficacy Variable

The primary efficacy variable measure in Studies DUR001-301 and DUR001-302 was clinical status at the EOT in the clinical evaluable (CE) population. A patient was defined as a clinical success based on the following:

- The patient's lesion size, as defined by erythema, had decreased from baseline;
- The patient's temperature was ≤37.6^{o} C (by any measurement method).
- Local signs of fluctuance and localized heat/warmth were absent;
- Local signs of tenderness to palpation and swelling/induration were no worse than mild; and
- For patients with a wound infection, the severity of purulent drainage was improved and no worse than mild relative to baseline.
- No need for further systemic antibacterial treatment for the SSTI.

In Study VER001-9, the primary efficacy variable was the clinical response (success, indeterminate, or failure, as assessed by investigator) in the CE population at TOC (Day 28).

- Clinical success was 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.

Regarding the timing of the assessment of the primary endpoint in the studies DUR001-301 and DUR001-302, this was discussed in the previously mentioned CHMP scientific advice (2010). Although usually the recommended time point for studies in cSSTI/ABSSSI is 7-10 days after the last day of treatment (*Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, EMA/CHMP/351889/2013*), it was agreed that the exceptionally slow elimination of dalbavancin may lead to unbalances between the treatment arms regarding active substance in the body at this time point. CHMP agreed in the above mentioned scientific advice that the primary efficacy variable should be evaluated at EOT. However, consistency between the outcome collected at EOT (=TOC) and at short-term follow-up (SFU) (day 28) in the different patient populations was considered essential. In general, the primary and secondary efficacy variables are endorsed and in line with current EU guidance, emphasising sufficient resolution of local and systemic signs and symptoms, such that the patient did not need any further systemic antibacterial treatment for the skin and skin structure infections.

Efficacy data and additional analysis

Demographic characteristics

The demographic characteristics were evenly distributed between the two treatment groups in both of the studies and also across the studies. The majority of the patients were males, whites, had creatinine clearance ≥ 30 mL/min, an elevated mean BMI and fever at baseline.

The number of patients hospitalised at study entry was:

DUR001-301: Dalbavancin group: 173 patients (75.2%) vs. vancomycin/linezolid group: 177 patients (75.0%).

DUR001-302: Dalbavancin group: 242 patients (70.1%) vs. vancomycin/linezolid group: 249 patients (71.8%).

Disease characteristics

Local signs of infection at baseline

DUR001-301: in the ITT population, local signs of infection at baseline were similar between the two treatment groups (table below).

Table 6 DUR001-301 – Local signs of infection at baseline (ITT and CE-EOT populations)

Local Signs of Infection	ITT Population Treatment Group			CE-EOT Population Treatment Group		
	Dalbavancin (N=288) n (%)	Vancomycin/Linezolid (N=285) n (%)	p-value	Dalbavancin (N=246) n (%)	Vancomycin/Linezolid (N=243) n (%)	p-value
Purulent drainage/discharge, N1	282	279	0.469	245	240	0.450
Absent	131 (46.5)	137 (49.1)		120 (49.0)	123 (51.3)	
Mild	36 (12.8)	25 (9.0)		31 (12.7)	20 (8.3)	
Moderate	61 (21.6)	57 (20.4)		49 (20.0)	47 (19.6)	
Severe	54 (19.1)	60 (21.5)		45 (18.4)	50 (20.8)	
Nonpurulent drainage/discharge (serous, sanguineous), N1	282	279	0.124	245	240	0.162
Absent	182 (64.5)	195 (69.9)		161 (65.7)	169 (70.4)	
Mild	47 (16.7)	28 (10.0)		40 (16.3)	23 (9.6)	
Moderate	45 (16.0)	45 (16.1)		39 (15.9)	41 (17.1)	
Severe	8 (2.8)	11 (3.9)		5 (2.0)	7 (2.9)	
Erythema, N1	282	279	0.958	245	240	0.904
Mild	9 (3.2)	9 (3.2)		8 (3.3)	7 (2.9)	
Moderate	82 (29.1)	78 (28.0)		68 (27.8)	63 (26.3)	
Severe	191 (67.7)	192 (68.8)		169 (69.0)	170 (70.8)	
Fluctuance, N1	282	279	0.128	245	240	0.191
Absent	164 (58.2)	171 (61.3)		152 (62.0)	155 (64.6)	
Mild	33 (11.7)	23 (8.2)		24 (9.8)	17 (7.1)	
Moderate	50 (17.7)	62 (22.2)		39 (15.9)	49 (20.4)	
Severe	35 (12.4)	23 (8.2)		30 (12.2)	19 (7.9)	
Heat/localized warmth, N1	282	279	0.521	245	240	0.279
Absent	0	1 (0.4)		0	1 (0.4)	
Mild	14 (5.0)	9 (3.2)		12 (4.9)	6 (2.5)	
Moderate	103 (36.5)	98 (35.1)		89 (36.3)	81 (33.8)	
Severe	165 (58.5)	171 (61.3)		144 (58.8)	152 (63.3)	
Tenderness to palpation, N1	282	279	0.402	245	240	0.571
Absent	1 (0.4)	3 (1.1)		1 (0.4)	2 (0.8)	
Mild	16 (5.7)	9 (3.2)		13 (5.3)	7 (2.9)	
Moderate	83 (29.4)	87 (31.2)		71 (29.0)	73 (30.4)	
Severe	182 (64.5)	180 (64.5)		160 (65.3)	158 (65.8)	
Swelling/induration, N1	282	279	0.488	245	240	0.552
Absent	0	0		0	0	
Mild	22 (7.8)	16 (5.7)		18 (7.3)	13 (5.4)	
Moderate	90 (31.9)	99 (35.5)		73 (29.8)	80 (33.3)	
Severe	170 (60.3)	164 (58.8)		154 (62.9)	147 (61.3)	

Source: Table 14.2.6.1, Table 14.2.6.3

Note: The percentages were based on the number of all patients or patients with each infection type and with nonmissing data (N1), unless otherwise stated.

[a] p-value is from a Fisher exact test.

DUR001-302:

Overall, in the ITT population, local signs of infection at baseline were generally similar between the two treatment groups.

Table 7 DUR001-302 – Local signs of infection at baseline (ITT and CE-EOT populations)

Local Signs of Infection	ITT Population Treatment Group			CE-EOT Population Treatment Group		
	Dalbavancin (N=371) n (%)	Vancomycin/ Linezolid (N=368) n (%)	*P* Value[a]	Dalbavancin (N=324) n (%)	Vancomycin/ Linezolid (N=302) n (%)	*P* Value[a]
Purulent drainage/discharge, N1	366	367	0.236	322	302	0.266
Absent	215 (58.7)	215 (58.6)		195 (60.6)	186 (61.6)	
Mild	50 (13.7)	43 (11.7)		42 (13.0)	33 (10.9)	
Moderate	61 (16.7)	79 (21.5)		49 (15.2)	59 (19.5)	
Severe	40 (10.9)	30 (8.2)		36 (11.2)	24 (7.9)	
Nonpurulent drainage/discharge (serous, sanguineous), N1	366	367	0.016	322	302	0.048
Absent	248 (67.8)	247 (67.3)		221 (68.6)	209 (69.2)	
Mild	67 (18.3)	55 (15.0)		57 (17.7)	49 (16.2)	
Moderate	35 (9.6)	58 (15.8)		28 (8.7)	39 (12.9)	
Severe	16 (4.4)	7 (1.9)		16 (5.0)	5 (1.7)	
Erythema, N1	366	367	0.796	322	302	0.549
Mild	12 (3.3)	9 (2.5)		11 (3.4)	7 (2.3)	
Moderate	176 (48.1)	175 (47.7)		159 (49.4)	142 (47.0)	
Severe	178 (48.6)	183 (49.9)		152 (47.2)	153 (50.7)	
Fluctuance, N1	366	367	0.896	322	302	0.831
Absent	211 (57.7)	214 (58.3)		188 (58.4)	180 (59.6)	
Mild	39 (10.7)	44 (12.0)		34 (10.6)	35 (11.6)	
Moderate	80 (21.9)	77 (21.0)		68 (21.1)	63 (20.9)	
Severe	36 (9.8)	32 (8.7)		32 (9.9)	24 (7.9)	
Heat/localized warmth, N1	366	367	0.221	322	302	0.087
Absent	1 (0.3)	0		1 (0.3)	0	
Mild	10 (2.7)	18 (4.9)		9 (2.8)	18 (6.0)	
Moderate	189 (51.6)	175 (47.7)		169 (52.5)	141 (46.7)	
Severe	166 (45.4)	174 (47.4)		143 (44.4)	143 (47.4)	
Tenderness to palpation, N1	366	367	0.272	322	302	0.240
Absent	0	2 (0.5)		0	2 (0.7)	
Mild	14 (3.8)	22 (6.0)		13 (4.0)	20 (6.6)	
Moderate	143 (39.1)	144 (39.2)		129 (40.1)	118 (39.1)	
Severe	209 (57.1)	199 (54.2)		180 (55.9)	162 (53.6)	
Swelling/induration, N1	366	367	0.701	322	302	0.798
Absent	3 (0.8)	1 (0.3)		2 (0.6)	1 (0.3)	
Mild	21 (5.7)	17 (4.6)		20 (6.2)	15 (5.0)	
Moderate	178 (48.6)	179 (48.8)		158 (49.1)	145 (48.0)	
Severe	164 (44.8)	170 (46.3)		142 (44.1)	141 (46.7)	

Source: Table 14.2.6.1 and Table 14.2.6.3.

Note: The percentages were based on the number of all patients or patients with each infection type and with nonmissing data (N1), unless otherwise stated.

[a] *P* value was from a Fisher exact test.

Abbreviations: CE-EOT = clinically evaluable at the end-of-treatment visit; ITT = intent-to-treat; n = number of patients with an observation; N = number of patients in the ITT or CE-EOT population; N1-number of patients with each local sign of infection.

The majority of patients in both treatment groups in study DUR001-301 had absence of purulent drainage/discharge and fluctuance. The signs of erythema, heat/localised warmth, tenderness to palpitation and swelling/induration were all classified as severe in most subjects.

For DUR001-302 the results were quite similar, except that compared to DUR001-301 the percentage of patients classified as moderate did not differ from the percentage categorised as severe for erythema, heat/localised warmth and swelling/induration. It therefore seems that the local signs of infection might be of lesser severity in this study compared to the observations made in DUR001-301.

Systemic signs of infection at baseline

DUR001-301: Systemic signs of infection at study entry were similar between the two treatment groups in both the ITT and the CE-EOT population.

Table 8 DUR001-301 - Systemic signs of infection at study entry (ITT and CE-EOT populations)

	ITT Population Treatment Group n1/n (%)			CE-EOT Population Treatment Group n1/n (%)		
	Dalbavancin (N=288)	Vancomycin/ Linezolid (N=285)	p-value[a]	Dalbavancin (N=246)	Vancomycin/ Linezolid (N=243)	p-value[a]
Patients with temperature ≥38°C, n1/n (%)	243/284 (85.6)	242/284 (85.2)	1.000	212/246 (86.2)	210/243 (86.4)	1.000
Patients with WBC >12,000 cells/mm^3, n1/n (%)	98/259 (37.8)	104/254 (40.9)	0.527	90/227 (39.6)	93/219 (42.5)	0.564
Patients with bands ≥10%, n1/n (%)	63/238 (26.5)	66/244 (27.0)	0.918	57/206 (27.7)	58/208 (27.9)	1.000
Patients with temperature ≥38°C only	147/288 (51.0)	138/285 (48.4)	0.559	123/246 (50.0)	118/243 (48.6)	0.786
Patients with WBCs >12,000 cells/mm^3 only	32/288 (11.1)	34/285 (11.9)	0.794	30/246 (12.2)	29/243 (11.9)	1.000
Patients with bands ≥10% only	2/288 (0.7)	0/285	0.499	1/246 (0.4)	0/243	1.000
Patients with temperature ≥38°C or WBCs >12,000 cells/mm^3 or bands ≥10%	279/288 (96.9)	276/285 (96.8)	1.000	244/246 (99.2)	239/243 (98.4)	0.448
Patients with temperature ≥38°C and either WBCs >12,000 cells/mm^3 or bands ≥10%	96/288 (33.3)	104/285 (36.5)	0.432	89/246 (36.2)	92/243 (37.9)	0.709
Patients with temperature ≥38°C and WBCs >12,000 Cells/mm^3 and bands ≥10%	27/288 (9.4)	32/285 (11.2)	0.494	25/246 (10.2)	30/243 (12.3)	0.476
Elevated hs-CRP (mg/L), n/N1 (%)[b]	253/284 (89.1)	258/284 (90.8)	0.577	218/246 (88.6)	219/243 (90.1)	0.661
Presence of regional lymphadenitis, n/N1 (%)[b]	62/288 (21.5)	73/285 (25.6)	0.279	58/246 (23.6)	69/243 (28.4)	0.257
Patients who meet SIRS criteria, n/N1 (%)[b]	175/284 (61.6)	175/284 (61.6)	1.000	159/246 (64.6)	156/243 (64.2)	0.925

Source: Table 14.2.6.6, Table 14.2.6.8

Note: The percentages were based on nonmissing data, unless otherwise stated. Meeting SIRS criteria is defined as having 2 or more of the following: temperature <36°C or >38°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute, or WBC count <4,000 cells/mm^3 or >12,000 cells/mm^3 or >10% bands. The values reported by the local laboratory were used to determine SIRS.

[a] p-value is from a Fisher exact test for dichotomous variables.

[b] Denominator n1 is the number of patients with nonmissing values.

Abbreviations: CE-EOT = clinically evaluable at the end-of-treatment visit; hs-CRP = high sensitivity C-reactive protein; ITT = intent-to-treat; n = number of patients with an observation; Max = maximum value; Min = minimum value; N = number of patients in the ITT or CE-EOT population; N = number of patients in the CE-EOT or ITT population; n = number of patients with an observation; n1 = number of patients with each systemic sign of infection; SIRS = systemic inflammatory response syndrome; WBC = white blood cell

DUR001-302:

Systemic signs of infection at study entry were similar between the two treatment groups in both the ITT and the CE-EOT population.

Table 9 DUR001-302 - Systemic signs of infection at study entry (ITT and CE-EOT populations)

	ITT Population Treatment Group			CE-EOT Population Treatment Group		
	Dalbavancin (N=371)	Vancomycin/ Linezolid (N=368)	*P* Value[a]	Dalbavancin (N=324)	Vancomycin/ Linezolid (N=302)	*P* Value[a]
Patients with temperature ≥38°C, n1/n (%)	306/365 (83.8)	310/365 (84.9)	0.760	271/322 (84.2)	255/299 (85.3)	0.738
Patients with WBC >12,000 cells/mm^3, n1/n (%)	149/368 (40.5)	146/367 (39.8)	0.880	130/324 (40.1)	125/302 (41.4)	0.807
Patients with bands ≥10%, n1/n (%)	48/241 (19.9)	42/234 (17.9)	0.640	45/214 (21.0)	36/193 (18.7)	0.619
Patients with temperature ≥38°C only	199/371 (53.6)	207/368 (56.3)	0.506	177/324 (54.6)	164/302 (54.3)	0.936
Patients with WBC >12,000 cells/mm^3 only	45/371 (12.1)	52/368 (14.1)	0.447	39/324 (12.0)	42/302 (13.9)	0.552
Patients with bands ≥10% only	3/371 (0.8)	2/368 (0.5)	1.000	3/324 (0.9)	2/302 (0.7)	1.000
Patients with temperature ≥38°C or WBC > 12,000 cells/mm^3 or bands ≥10%	365/371 (98.4)	368/368 (100.0)	0.031	323/324 (99.7)	302/302 (100.0)	1.000
Patients with temperature ≥38°C and either WBC > 12,000 cells/mm^3 or bands ≥10%	107/371 (28.8)	103/368 (28.0)	0.807	94/324 (29.0)	91/302 (30.1)	0.793
Patients with temperature ≥38°C and WBC > 12,000 cells/mm^3 and bands ≥10%	20/371 (5.4)	23/368 (6.3)	0.641	19/324 (5.9)	20/302 (6.6)	0.742
Elevated hs-CRP (mg/L), n/N1 (%)[b]	332/366 (90.7)	327/367 (89.1)	0.540	291/322 (90.4)	274/302 (90.7)	0.892
Presence of regional lymphadenitis, n/N1 (%)[b]	43/363 (11.8)	46/365 (12.6)	0.821	41/321 (12.8)	37/299 (12.4)	0.904
Patients who met SIRS criteria, n/N1 (%)[b]	157/368 (42.7)	161/368 (43.8)	0.823	137/324 (42.3)	134/302 (44.4)	0.628

Source: Table 14.2.6.6 and Table 14.2.6.8.
Note: The percentages were based on nonmissing data, unless otherwise stated. Meeting SIRS criteria was defined as having 2 or more of the following: temperature <36°C or >38°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute, or WBC count <4,000 cells/mm^3 or >12,000 cells/mm^3 or >10% bands. The values reported by the local laboratory were used to determine SIRS.
[a] *P* value was from a Fisher exact test for dichotomous variables.
[b] Denominator N1 was the number of patients with nonmissing values.
Abbreviations: CE-EOT = clinically evaluable at the end-of-treatment visit; hs-CRP = high sensitivity C-reactive protein; ITT = intent-to-treat; n=number of patients with an observation; n1= number of patients with each systemic sign of infection; N = number of patients in the ITT or CE-EOT population; SIRS = systemic inflammatory response syndrome; WBC = white blood cells.

For both studies DUR001-301 and 302 the results show that almost all patients had 1 of the systemic signs in both treatment groups. Around 30-40% had 2 signs and app. 10% had 3 signs in both treatment groups in DUR001-301. For DUR001-302 the corresponding numbers were app. 30% and around 5-6%, respectively. In study DUR001-301 around 60% met the SIRS criteria (both treatment groups) while this was the case for ca. 40% in DUR001-302. When looking at the infection type cellulitis, major abscess and wound infection the majority of patients fulfilled the temperature criterion in both treatment groups for both studies. Across infection types patients with major abscess were least likely to fulfil this criterion in both treatment groups in both studies.

Low numbers of patients had all 3 signs of systemic infection and this was similar between infection types, treatment groups and studies.

In order to ensure that the included infections could be defined as complicated, not only the size of the lesion area is of importance, also the depth of the soft tissue involvement (subcutaneous tissue, fascia plane and muscle) is a critical parameter. The applicant has clarified that the depth of the infections was assessed only in a minority of the included patients. It was also noted that no requirement to provide specific information on this is mentioned in the CHMP guideline on antibacterials.

Outcome

In studies DUR001-301 and DUR001-302, approximately 90% of subjects within each treatment group completed the study and the percentages of subjects either discontinuing from the study or withdrew from study drug were relatively well balanced across treatment groups within each study. In study VER001-9, there were however some imbalances regarding subjects who were withdrawn due to worsening of clinical status, disfavouring the dalbavancin group.

When assessing data from a clinical phase 3 study, the issue whether the external validity of the study is acceptable, i. e. that a sufficient number of patients with representative disease entities and severe disease requiring IV therapy was included and is accessible for evaluation, is crucial.

CHMP noted that a considerably higher proportion of patients in studies DUR001-301 and -302 were recruited in Europe (close to 60%) compared to the first Phase 3 study, VER001-9 (approximately 15%).

A summary of the number and percentage of subjects in each population by pivotal study is shown below:

Table 10 Populations for Analysis in Each Pivotal Study

	Pivotal Studies					
	DUR001-301 (cSSTI)		DUR001-302 (cSSTI)		VER001-9 (cSSTI)	
	Dalba-vancin N = 288	Vanco-mycin/ Linezolid N = 285	Dalba-vancin N = 371	Vanco-mycin/ Linezolid N = 368	Dalba-vancin N = 571	Linezolid N = 283
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ITT	288	285	371	368	571	283
ITT, excluding indeterminates	274 (95.1)[a]	276 (96.8)[a]	361 (97.3)[a]	348 (94.5)[a]	486 (85.1)	254 (89.8)
Day 10-14						
CE-EOT	246 (85.4)	243 (85.3)	324 (87.3)	302 (82.1)	NA	NA
CE at EOT	NA	NA	NA	NA	457 (80.0)	243 (85.9)
Day 28						
CE-SFU	226 (78.5)	229 (80.4)	294 (79.2)	272 (73.9)	NA	NA
CE at TOC	NA	NA	NA	NA	434 (76.0)	226 (79.9)
Day 39						
CE at TOC	NA	NA	NA	NA	298 (94.3)[d]	151 (92.6)[d]
Day 70						
CE-LFU	219 (76.0)	212 (74.4)	280 (75.5)	267 (72.6)	NA	NA
MicroITT	153 (53.1)	155 (54.4)	184 (49.6)	174 (47.3)	358 (62.7)	192 (67.8)
Modified MicroITT	NA	NA	NA	NA	NA	NA
ME-EOT	123 (42.7)	128 (44.9)	156 (42.0)	131 (35.6)	NA	NA
ME at EOT[e]	NA	NA	NA	NA	288 (80.4)	164 (85.4)
ME at TOC[e]	NA	NA	NA	NA	277 (77.4)	152 (79.2)

a) Indeterminates = Indeterminate at EOT
b) The percentage was based on the number of subjects with clinical response at TOC.
c) The percentage was based on number of subjects in the MicroITT population.

The reasons for exclusion from the clinically evaluable populations in studies DUR001-301 and -302 were similar in all treatment groups. In study VER001-9, there was higher proportion of patients excluded from the CE

population in the dalbavancin group leading to indeterminate response, and of patients who received <72 hours of study drug (6.3% vs. 1.4% at TOC). Besides any potential effect on the outcome of the primary endpoint caused by this imbalance, this also indicates that many of the patients were not severally ill enough at baseline, since they required less than 3 days IV therapy.

Study drug exposure

Due to the short half-life of dalbavancin, each dose of dalbavancin was assigned a duration of 7 days' worth of treatment in the phase 3 program. Subjects receiving dalbavancin were more likely than subjects receiving vancomycin/linezolid to receive a shorter duration of blinded treatment (i.e., including placebo), with a greater proportion of dalbavancin subjects than vancomycin/linezolid subjects receiving 10 days of treatment (20.8% vs. 15.3%). Of those subjects completing 10 to 14 days of therapy, fewer dalbavancin than vancomycin/linezolid subjects received more than 10 days of therapy (27.2% vs. 34.3%).

The pooled data from the DUR001-301 and DUR001-302 studies showed that 1260 (96.6%) of patients received ≥ 72 hours of intravenous study drug therapy.

Characteristics of patient populations

In the phase 3 studies DUR001-301 and -302 the most common category of infection was cellulitis (52% to 55%) in contrast to study VER001-9 where little less than 30% were categorized as cellulitis. In that study there was a category of deep soft tissue infection (approximately 16%). Major cutaneous abscess constituted 24% to 30% in the two more recent studies, similar as in the older study (major abscess approximately 30%), which is in line with current CHMP guidance (*Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, EMA/CHMP/351889/2013*) which recommends that the proportion of patients enrolled with abscess should be limited to approximately 30%. Further, the Addendum requires that patients should demonstrate a protocol-defined minimum number of signs and symptoms associated with an ongoing acute infectious process; this criterion was generally fulfilled for the patients included in these two, more recently performed studies. See further discussion on outcome based on the presence of systemic signs of infection and SIRS criteria.

The number of patients with Gram-positive bacteraemia was low in both treatment groups in each of the two pivotal studies. In DUR001-301 a total of 8 cases in the dalbavancin group vs. 6 cases in the vancomycin/linezolid group were observed. The corresponding numbers for DUR001-302 were a total of 21 cases in the dalbavancin group compared to 11 in the vancomycin/linezolid group. In study VER001-9 there were 12 bacteraemic cases in the dalbavancin group and 6 patients in the comparator group.

In study DUR001-301 around 15% in the dalbavancin group vs. ca. 10% in the vancomycin/linezolid group had an established diagnosis of diabetes mellitus. In DUR001-302 there were fewer patients in the dalbavancin group with this diagnosis (around 10% vs. ca. 17% in the comparator group).

In both studies the number of patients with peripheral arterial disease was also scarce (1%).

In study VER001-9, 23% of the overall population had diabetes, and vascular disease was present in 9% of the overall VER001-9 population. These figures are higher than for studies DUR001-301 and DUR001-302. Nevertheless, the inclusion criteria did not specifically require adequate systemic signs of infection, and no detailed data for e.g. SIRS were presented, which led the CHMP to question at the time of the previous marketing authorisation the adequacy of the included patients in terms of severity in the former MAA procedure. This is the reason why the results of this study could only be considered as supportive for this marketing authorisation application.

Distribution of pathogens

The most commonly isolated pathogen in the three pivotal studies was *Staphylococcus aureus*, of which MRSA ranged from 65 to 81%, followed by *Streptococcus pyogenes*. In addition other isolated pathogens belonging to various species, were judged as pathogens and associated with the skin and skin structure infections by the applicant. This is generally consistent with what is expected from this target population. Of note, the number of *S. pyogenes* was unexpectedly low in particular in study DUR001-301 and VER-001-9. During the procedure, the CHMP asked the applicant to discuss this rather low number of *S. pyogenes* and it was accepted and supported by external evidence that a lower yield of *S. pyogenes* can be expected in the cultures. The serological data confirmed that dalbavanicn was effective in these cases. The distribution of the pathogens isolated from the primary site of infection at baseline was similar in both treatment groups.

Table 11 Baseline Pathogens in the MicroITT Population in Each Pivotal Study, n (%)

	DUR001-301 (cSSTI)		**DUR001-302 (cSSTI)**		**VER001-9 (cSSTI)**	
	Dalbavancin	**Vancomycin / Linezolid**	**Dalbavancin**	**Vancomycin / Linezolid**	**Dalbavancin**	**Linezolid**
All Baseline isolates	166	175	209	199	391	215
Staphylococcus aureus (all)	122 (73.5)	128 (73.1)	135 (64.6)	129 (64.8)	318 (81.3)	174 (80.9)
MRSA	44 (26.5)	39 (22.3)	46 (22.0)	28 (14.1)	181 (46.3)	97 (45.1)
MSSA	78 (47.0)	88 (50.3)	89 (42.6)	101 (50.8)	0	0
Streptococcus pyogenes	12 (7.2)	14 (9.6)	25 (12.0)	22 (11.0)	19 (4.9)	12 (5.6)
Coagulase-negative staphylococci[a]	0	0	3 (1.4)	1 (0.5)	0	0
Viridans streptococcus NOS*	0	0	0	0	8 (2.0)	3 (1.4)
Streptococcus mitis	0	1 (0.6)	0	1 (0.5)	1 (0.3)	0 (0)
Streptococcus oralis	0	0	0	0	2 (0.5)	0 (0)
Streptococcus sanguis	0	0	0	0	1 (0.3)	0 (0)
Viridans Strep	2 (1.2)	3 (1.7)	5 (2.4)	3 (1.5)	4 (1.0)*	0*
Streptococcus anginosus Group	0	0	0	0	3 (0.8)	3 (1.4)
S. anginosus	2 (1.2)	3 (1.7)	4 (1.9)	1 (0.5)	0 (0)	1(0.5)
Streptococcus constellatus	5 (3.0)	8 (4.6)	10 (4.8)	8 (4.0)	1 (0.3)	1 (0.5)
Streptococcus intermedius	0	3 (1.7)	6 (2.9)	4 (2.0)	0	0
β-hemolytic streptococcus	0	0	0	0	1 (0.3)*	0 (0)*
Strep Group B	0	0	0	0	0	0
Strep Group C	5 (3.0)	2 (1.1)	0	3 (1.5)	5 (1.3)	3 (1.4)
Strep Group G	0	1 (0.6)	0	2 (1.0)	10 (2.6)	6 (2.8)
Streptococcus agalactiae	3 (1.8)	6 (3.4)	9 (4.3)	8 (4.0)	16 (4.1)	10 (4.7)
Streptococcus bovis	0	0	0	1 (0.5)	0	0
Streptococcus dysgalactiae	0	0	3 (1.4)	1 (0.5)	1 (0.3)	0 (0)
Streptococcus gordonii	0	0	1 (0.5)	0	0	0
Streptococcus mutans	0	0	0	1 (0.5)	0	0

	DUR001-301 (cSSTI)		DUR001-302 (cSSTI)		VER001-9 (cSSTI)	
	Dalbavancin	Vancomycin / Linezolid	Dalbavancin	Vancomycin / Linezolid	Dalbavancin	Linezolid
Streptococcus salivarius	1 (0.6)	0	0	0	0	0
Streptococcus pneumoniae	1 (0.6)	0	0	0	0	0
Streptococcus sp.	0	0	0	1 (0.5)	0	0
Aerococcus viridans	0	0	0	1 (0.5)	0	0
Arcanobacterium haemolyticum	0	0	1 (0.5)	0	0	0
Enterococcus faecalis	3 (1.8)	5 (2.9)	9 (4.3)	8 (4.0)	0	0
Enterococcus faecium	1 (0.6)	0	0	1 (0.5)	0	0
Eubacterium lentum	0	0	0	1 (0.5)	0	0
Finegoldia magna	0	1 (0.6)	1 (0.5)	1 (0.5)	0	0
Peptoniphilus asaccharolyticus	1 (0.6)	0	0	1 (0.5)	0	0
Clostridium clostridioforme	0	0	1 (0.5)	0	0	0
Clostridium hastiforme	0	0	1 (0.5)	0	0	0
Clostridium perfringens	0	1 (0.6)	1 (0.5)	1 (0.5)	1 (0.3)	0 (0)
Clostridium sporogenes	0	0	1 (0.5)	0	0	0
Corynebacterium jeikeium	0	0	0	0	2 (0.5)	0 (0)
Peptostreptococcaceae	0	0	0	0	3 (0.8)**	4 (1.9)**
Peptostreptococcus sp.	0	0	0	1 (0.5)	0	0
Peptostreptococcus anaerobius	0	0	1 (0.5)	0	0	0
Peptostreptococcus micros	0	0	0	1 (0.5)	0	0
Propionibacterium acnes	0	0	2 (1.0)	2 (1.0)	0	0

The CHMP advised the company in the scientific advice given to focus the recruitment in areas with high prevalence of MRSA. Despite the fact that this recommendation seems to have been fulfilled as in several of the listed countries the probability of finding patients with infections caused by MRSA is expected to be rather high, the final results showed a relatively low frequency of MRSA in both pivotal trials (< 30%). Nevertheless, CHMP agreed that the frequency of MRSA was not lower than what had been accepted earlier from similar marketing authorisation applications for approved in the same indication.

The patients in the two studies had mainly monomicrobial infections. However, in DUR001-301 this comprised more patients in the dalbavancin group (87.6%) compared to the comparator group (77.4%) and also when compared to both treatment groups in study DUR001-302 (dalbavancin group 71.2% of patients and in the vancomycin/linezolid group 71.3% of patients). This could potentially favour the result of the dalbavancin arm in DUR001-301.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk

assessment (see later sections).

Table 12 Summary of efficacy for study **DUR001-301**

Title: A Phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin and linezolid) for the treatment of acute bacterial skin and skin structure infections			
Study identifier	**DUR001-301**		
Design	Randomized (1:1 ratio), double-blind, pharmacist-unblinded, pivotal study		
	Duration of main phase: Duration of run-in phase: Duration of Extension phase:	April 2011 to November 2012. The total duration of the study was a minimum of 61 days and a maximum of 89 days. not applicable not applicable	
Hypothesis	Non-inferiority		
Treatments groups	Dalbavancin IV + placebo p.o.	Dalbavancin, 1000 mg day 1, 500 mg day 7, with the option to switch to oral placebo; duration 10 to 14 days inclusive oral placebo; number randomized n=288 (ITT)	
	Vancomycin IV + linezolid p.o.	Vancomycin, 1000 mg or 15 mg/kg q12h, with the option to switch to oral linezolid, 600 mg q12h; duration: 10-14 days number randomized: n=285 (ITT)	
Endpoints and definitions	Primary endpoint	Clinical success at EOT in the CE population	
	Secondary endpoints	-Clinical success at EOT in the ITT population -Clinical response at 48-72hours post study drug initiation in the ITT population	
	Other endpoint	Clinical success at SFU in the CE population	
Database lock	November 2012		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: 573; Per protocol (CE at EOT): 489		
Descriptive statistics and estimate variability	Treatment group	dalbavancin	Vancomycin/linezolid
	Number of subject	246	243
	Primary endpoint (clinical success at EOT)	214/246 (87%)	222/243 (91.4%)
	% treatment difference; (95% CI)	-4.4; (-9.6, 1.6)	

	Secondary endpoint: Clinical response at 48-72hours post study drug initiation in the ITT population (%)	240/288 (83.3%)	233/285 (81.8%)
	% treatment difference; (95% CI)	1.5; (-4.6, 7.9)	
	Other endpoint: Clinical success at SFU (day 28) (%)	212/226 (93.8%)	220/229 (96.1%)
	% treatment difference; (95% CI)	-2.3; (-6.8, 1.9)	

Table 13 Summary of efficacy for study **DUR001-302**

Title: A Phase 3, randomized, double-blind, double-dummy study to compare the efficacy and safety of dalbavancin to a comparator regimen (vancomycin and linezolid) for the treatment of acute bacterial skin and skin structure infections		
Study identifier	**DUR001-302**	
Design	Randomized (1:1 ratio), double blind, pharmacist-unblinded, pivotal study	
	Duration of main phase:	September 2011 to December 2012. The total duration of the study was a minimum of 61 days and a maximum of 89 days.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Non-inferiority	
Treatments groups	Dalbavancin IV + placebo p.o.	Dalbavancin, 1000 mg day 1, 500 mg day 7, with the option to switch to oral placebo; duration 10 to 14 days inclusive oral placebo; number randomized n=288 (ITT)
	Vancomycin IV + linezolid p.o.	Vancomycin, 1000 mg or 15 mg/kg q12h, with the option to switch to oral linezolid, 600 mg q12h; duration 10-14 days: number randomized n=285 (ITT)
Endpoints and definitions	Primary endpoint	Clinical success at EOT in the CE population
	Secondary endpoints	-Clinical success at EOT in the ITT population -Clinical response at 48-72hours post study drug initiation in the ITT population
	Other endpoint	Clinical success at SFU in the CE population
Database lock	27 December 2012	

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: 739; Per protocol (CE at EOT): 626		
Descriptive statistics and estimate variability	Treatment group	dalbavancin	Vancomycin/linezolid
	Number of subject	324	302
	Primary endpoint (%clinical success)	303/324 (93.5%)	280/302 (92.7%)
	% treatment difference; (95% CI)	0.8; (-3.3, 4.9)	
	Secondary endpoint: Clinical response at 48-72hours post study drug initiation in the ITT population (%)	285/371 (76.8%)	288/368 (78.3%)
	% treatment difference; (95% CI)	-1.5; (-7.4, 4.6)	
	Other endpoint: Clinical success at SFU (day 28) (%)	283/294 (96.3%)	257/272 (94.5%)
	% treatment difference; (95% CI)	1.8; (-1.8, 5.6)	

Table 14 Summary of efficacy for study **VER001-9**

Title: Phase 3, Randomized, Double-Blind, Multi-Centre Study to Evaluate the Safety and Efficacy of Dalbavancin Versus Linezolid in the Treatment of Complicated Skin and Soft Tissue Infections* with Suspected or Confirmed Gram- Positive Bacterial Pathogens		
Study identifier	**VER001-9**	
Design	A randomized, double-blind (third party unblinded), multi-centre study enrolled patients with complicated SSSI. Eligible patients were randomized 2:1 (dalbavancin:linezolid)	
	Duration of main phase:	Date first subject enrolled: 3 January 2003 Date last subject completed: 21 May 2004 Treatment duration: 14 days (IV plus oral)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	Non-inferiority	
Treatments groups	Dalbavancin (IV)	1000 mg dose on Day 1 followed by a 500 mg dose on Day 8; number randomized: n=571
	Linezolid (IV/oral)	IV linezolid: 600 mg q 12 h, possible switch to oral linezolid 600 mg q 12 h; number randomized n= 283
Endpoints and definitions	Primary endpoint:	Clinical response at TOC (14+/- 2 days after completion of therapy) in the CE population
	Secondary endpoint	Clinical response at TOC in the ITT population
Database lock	May 2004	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol time point: TOC= 14+/- 2 days after completion of therapy		
Descriptive statistics and estimate variability	Treatment group	dalbavancin	linezolid
	Number of subject	n=434	n=226
	Primary endpoint Clinical response rate at TOC in CE population (%)	386/434 (88.9%)	206/226 (91.2%)
	% treatment difference; (95% CI)	-2.21; (-7.28, 2.86)	
	Secondary endpoint: Clinical response rate at TOC in the ITT population (including indeterminants) (%)	437/571 (76.5%)	234/283 (82.7%)
	% treatment difference; (95% CI)	-6.15; (-12.03, -0.27)	

Microbiological response by pathogen

By-pathogen microbiological response at EOT in the ME population is summarized for each phase 3 study below for Gram-positive aerobes (including *S. aureus*, MRSA, MSSA) and Gram-positive anaerobes. The by-pathogen microbial response provides additional important data, indicating non-inferiority to the comparator in important species, as supported by *in vitro* microbiology data.

Table 15 By-Pathogen Microbiological Response at EOT in the ME Population: Study DUR001-301

	Dalbavancin n (%)	**Vancomycin/Linezolid n (%)**
ME population, N	123	128
Gram-positive aerobes	N = 125	N = 137
Success[a]	110 (88.0)	125 (91.2)
Failure	15 (12.0)	12 (8.8)
Staphylococcus aureus	N = 101	N = 109
Success	89 (88.1)	99 (90.8)
Failure	12 (11.9)	10 (9.2)
MRSA[a]	N = 35	N = 31
Success	31 (88.6)	30 (96.8)
Failure	4 (11.4)	1 (3.2)
MSSA[b]	N = 66	N = 77
Success	58 (87.9)	68 (88.3)
Failure	8 (12.1)	9 (11.7)
Streptococcus pyogenes	N = 11	N = 12
Success	11 (100)	10 (83.3)
Failure	0	2 (16.7)
Streptococcus agalactiae	N = 1	N = 2
Success	0	2 (100)
Failure	1 (100)	0
Streptococcus anginosus	N = 2	N = 2
Success	2 (100.0)	2 (100)
Streptococcus intermedius	N = 0	N = 2
Success	0	2 (100.0)
Streptococcus constellatus	N = 4	N = 7
Success	4 (100.0)	7 (100.0)
Gram-positive anaerobes	N = 1	N = 1

Table 16 By-Pathogen Microbiological Response at EOT in the ME Population: Study DUR001-302

	Dalbavancin n (%)	**Vancomycin/ Linezolid n (%)**
ME population, N	156	131
Gram-positive aerobes	N = 173	N = 148
Success	164 (94.8)	140 (94.6)
Failure	9 (5.2)	8 (5.4)
Staphylococcus aureus	N = 118	N = 104
Success	112 (94.9)	99 (95.2)
Failure	6 (5.1)	5 (4.8)
MRSA[a]	N = 43	N = 24
Success	42 (97.7)	24 (100.0)
Failure	1 (2.3)	0
MSSA[a]	N = 75	N = 80
Success	70 (93.3)	75 (93.8)
Failure	5 (6.7)	5 (6.3)
Streptococcus pyogenes	N = 22	N = 20
Success	22 (100.0)	19 (95.0)
Failure	0	1 (5.0)
Streptococcus agalactiae	N = 7	N = 4
Success	6 (85.7)	3 (75.0)
Failure	1 (14.3)	1 (25.0)
Streptococcus anginosus	N = 3	N = 1
Success	3 (100.0)	1 (100.0)
Streptococcus intermedius	N = 4	N = 2
Success	3 (75.0)	2 (100.0)
Failure	1 (25.0)	0
Streptococcus constellatus	N = 6	N = 7
Success	5 (83.3)	6 (85.7)
Failure	1 (16.7)	01 (14.3)
Gram-positive anaerobes	N = 6	N = 5
Success	5 (83.3)	5 (100.0)
Failure	1 (16.7)	0

Table 17 By-Pathogen Microbiological Response at TOC: Study VER001-9

Population Pathogen	Dalbavancin n (%)	Linezolid n (%)
ME		
All Species	N = 301	N = 172
Success	268 (89.0)	150 (87.2)
S. aureus	N = 250	N = 141
Success	221 (88.4)	125 (88.7)
MRSA[a]	N = 146	N = 73
Success	133 (91.1)	65 (89.0)
MicroITT		
All Species	N = 391	N = 215
Success	305 (78.0)	170 (79.1)
Failure	86 (22.0)	45 (20.9)
Indeterminate[b]	52 (13.3)	23 (10.7)
S. aureus	N = 318	N = 174
Success	249 (78.3)	139 (79.9)
Failure	69 (21.7)	35 (20.1)
Indeterminate[b]	39 (12.3)	19 (10.9)
MRSA[a]	N = 181	N = 97
Success	145 (80.1)	75 (77.3)
Failure	36 (19.9)	22 (22.7)
Indeterminate[b]	22 (12.2)	14 (14.4)

[a] Indeterminate was a subset of a response of "failure."

Subgroup analyses

There was no indication on differences in clinical outcome between treatment groups in respect of baseline demographic characteristics such as age, gender, race or ethnicity.

Lower success rates were seen in countries outside North America and the European Union, specifically in some countries from Asia and South Africa, though the number of patients in those countries was small.

Analysis by infection type:

Table 18 Clinical Status at EOT by Infection Type in the CE-EOT and ITT Populations

	DUR001-301 (cSSTI)		DUR001-302 (cSSTI)	
Characteristic	**Dalbavancin n (%)**	**Vancomycin/ Linezolid n (%)**	**Dalbavancin n (%)**	**Vancomycin/ Linezolid n (%)**
CE-EOT	N = 246	N = 243	N = 324	N = 302
Infection type				
Cellulitis	142	129	182	172
Clinical success	127 (89.4)	122 (94.6)	167 (91.8)	154 (89.5)
Major abscess	54	69	79	70
Clinical success	50 (92.6)	65 (94.2)	75 (94.9)	68 (97.1)
Wound infection	50	45	63	60
Clinical success	37 (74.0)	35 (77.8)	61 (96.8)	58 (96.7)
Traumatic wound	50	44	53	53
Clinical success	37 (74.0)	34 (77.3)	51 (96.2)	51 (96.2)
Surgical site	0	1	10	7
Clinical success	0	1 (100.0)	10 (100.0)	7 (100.0)
ITT	N = 288	N = 285	N = 371	N = 368
Infection type				
Cellulitis	156	147	198	202
Clinical success	137 (87.8)	133 (90.5)	174 (87.9)	168 (83.2)
Major abscess	72	86	90	87
Clinical success	61 (84.7)	77 (89.5)	81 (90.0)	78 (89.7)
Wound infection	60	52	82	79
Clinical success	38 (63.3)	37 (71.2)	74 (90.2)	69 (87.3)
Traumatic wound	60	51	71	67
Clinical success	38 (63.3)	36 (70.6)	63 (88.7)	58 (86.6)
Surgical site	0	1	11	12
Clinical success	0	1 (100.0)	11 (100.0)	11 (91.7)

Severity of illness

Overall, in both the CE-EOT and CE-SFU populations, clinical outcomes were not different in the subgroup of patients who did or did not meet SIRS criteria at baseline. The applicant has provided sufficient information regarding the clinical status of the patients at baseline, related to outcome, including more detailed information of SIRS criteria.

Table 19 Clinical Success by SIRS criteria at Baseline: Studies DUR001-301 and DUR001-302

	DUR001-301			DUR001-302		
	Dalbavancin	**Vancomycin / Linezolid**	**Difference (95% CI)**	**Dalbavancin**	**Vancomycin / Linezolid**	**Difference (95% CI)**
CE-EOT Population	246	243		324	302	
Clinical Success at EOT						
Met SIRS Criteria	133 (83.7)	142 (91.0)	-7.4 (-14.9, 0.0)	124 (90.5)	121 (90.3)	0.2 (-7.1, 7.6)
Met SIRS Criteria – sensitivity analysis*	147 (92.5)	148 (94.9)	-2.4 (-8.1, 3.4)	123 (89.8)	125 (93.3)	-3.5 (-9.8, 4.4)
Did not meet SIRS Criteria – sensitivity analysis*	83 (95.4)	82 (94.3)	1.1 (-6.4, 9.0)	180 (96.3)	162 (96.4)	-0.1 (-4.8, 4.2)
Met SIRS criteria (with inclusion of regional lymphadenopathy) – sensitivity analysis*	160 (93.0)	163 (95.3)	-2.3 (-7.6, 3.1)	152 (91.0)	145 (93.6)	-2.6 (-8.3, 4.1)
Did not meet SIRS criteria (with inclusion of regional lymphadenopathy) - sensitivity analysis*	70 (94.6)	67 (93.1)	1.5 (-8.8, 9.5)	151 (96.2)	142 (96.6)	-0.4 (-5.7, 4.2)
CE-SFU Population	226	229		294	272	
Clinical Success at SFU						
Met SIRS criteria	136 (93.8)	146 (96.7)	-2.9 (-8.4, 2.3)	121 (96.0)	112 (91.8)	4.2 (-1.9, 11.0)
Did not meet SIRS criteria	76 (93.8)	74 (94.9)	-1.1 (-9.3, 7.2)	162 (96.4)	145 (96.7)	-0.3 (-4.7, 4.5)
Met SIRS Criteria – sensitivity analysis*	137 (94.5)	143 (94.7)	-0.2 (-6.1, 5.1)	122 (96.8)	113 (92.6)	4.2 (-0.8, 11.7)
Did not meet SIRS Criteria – sensitivity analysis*	75 (92.6)	74 (94.9)	-2.3 (-11.1, 6.1)	162 (96.4)	145 (96.7)	-0.3 (-5.1, 4.4)
Met SIRS criteria (with inclusion of regional lymphadenopathy) - sensitivity analysis*	151 (95.0)	158 (95.2)	-0.2 (-5.9, 4.5)	149 (97.4)	131 (93.6)	3.8 (-0.9, 9.8)
Did not meet SIRS criteria (with inclusion of regional lymphadenopathy) - sensitivity analysis*	61 (91.0)	59 (93.7)	-2.7 (-13.8, 7.0)	135 (95.7)	127 (96.2)	-0.5 (-6.2, 4.7)

Bacteraemia

There was no specific concern on efficacy in the subset of patients with bacteraemia associated to cSSTI. In the table below the outcome in patients with pathogens with major relevance for cSSTI isolated from blood (*S. aureus* and betahemolytic streptococci) are depicted.

Clinical success rates per pathogen at end of treatment in patients with *S. aureus* or betahemolytic streptococcal bacteraemia at baseline (ITT population)

Baseline pathogen in blood cultures	Dalbavancin n/N(%)	Vancomycin/Linezolid n/N(%)
DUR001-301		
Staphylococcus aureus	2/4 (50.0)	3/3 (100)
Streptococcus agalactiae	2/3 (66.7)	0
Streptococcus pyogenes	1/1 (100)	0
Streptococcus Group C	0	1/1 (100)
DUR001-302		
Staphylococcus aureus	5/7 (71.4)	5/6 (83.3)
Streptococcus pyogenes	2/3 (66.7)	1/1 (100)
Streptococcus agalactiae	2/2 (100)	1/1 (100)
Streptococcus dysgalactiae	0	1/1 (100)
VER001-9		
Staphylococcus aureus	5/8 (62.5)	2/3 (66.7)
Streptococcus agalactiae	1/1 (100)	1/2 (50.0)
Streptococcus pyogenes	1/1 (100)	1/1 (100)
Streptococcus Group C	1/1 (100)	0
Streptococcus Group G	0/1 (0.0)	0
Total	**22/32 (68.8)**	**16/19 (84.2)**

Subjects with history of Diabetes mellitus

Table 21 Clinical Success by history of Diabetes mellitus – Studies DUR001-301, DUR001-302 and VER001-9

	DUR001-301 (CE-EOT)		DUR001-302 (CE-EOT)		VER001-9 (CE-TOC)	
	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	Dalbavancin n/N (%)	Linezolid n/N (%)
Patients with Diabetes mellitus at Baseline	29/37 (78.4)	20/24 (83.3)	31/34 (91.2)	47/52 (90.4)	92/108 (85.2)	37/45 (82.2)
Difference (95% CI)	-4.9 (NA, NA)		0.8 (-15.4, 14.5)		NA	
Patients without Diabetes mellitus at Baseline	185/209 (88.5)	202/219 (92.2)	272/290 (93.8)	233/250 (93.2)	294/326 (90.2)	169/181 (93.4)
Difference (95% CI)	-3.7 (-9.4, 1.9)		0.6 (-3.5, 5.2)		NA	

Short-term follow-up (SFU) and long-term follow-up (LFU) visits

The proportion of patients assessed by the investigator as a clinical success at EOT or SFU in any of the populations analyzed were similar between the two treatment groups for both studies.

Very few patients were deemed as relapse/recurrence at the LFU visit; in DUR001-301 one patient from the vancomycin/linezolid was considered a relapse/recurrence while in DUR001-302 one patient from the dalbavancin group was considered the same.

Based on these results it seems that for the remaining patients that were clinical successes at SFU the effect persists also until LFU for both dalbavancin and vancomycin/linezolid in both pivotal studies.

The applicant stated that at the LFU assessment serum levels of dalbavancin would be approximately 3 mg/L. Considering that MIC_{90s} of 0.06 mg/L for staphylococci and 0.03 – 0.06 mg/L for streptococci have been observed for dalbavancin, this implies that at the time point for LFU, therapeutic levels of dalbavancin are still present in the body. The potential for relapses when therapeutic levels of dalbavancin are no longer present was therefore not studied. However, this is not considered necessary because the slow elimination of dalbavancin would likely decrease the risk for relapses. Furthermore, the timing of the evaluation has been agreed by the CHMP in previous scientific advice.

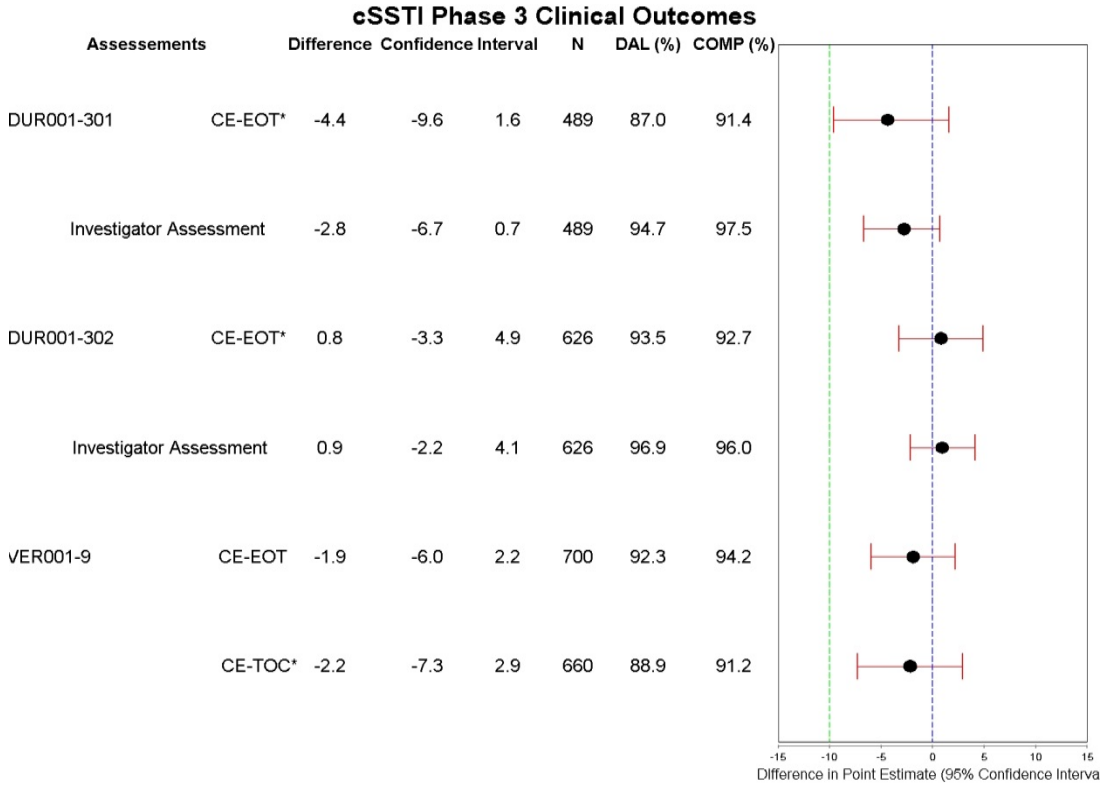
Clinical studies in special populations

There were no clinical efficacy studies in special populations.

Analysis performed across trials (pooled analyses AND meta-analysis)

In two of the three pivotal studies (DUR001-301 and VER001-9), the point estimates for the primary endpoint were numerically lower in the dalbavancin arms, whereas in study DUR001-302 the point estimate for the primary endpoint was higher in the dalbavancin arm as opposed to the comparator arm. In all studies, the lower value of the 95% CI was within the predefined range.

Figure 3 Success Rate and 95% Confidence Interval on the Treatment Difference at the Primary Endpoint and Investigator Assessment at EOT for Phase 3 Studies



*Primary endpoint; Abbreviations: EOT = end of treatment; TOC = test of cure; VER001-9 Table 2.1; DUR001-301 CSR; DUR001-302 CSR

Supportive studies

There were three supportive studies (VER001-16, VER001-8 and VER001-5) which were conducted in the indication complicated or uncomplicated SSTI. All these studies were assessed during the former MAA procedure in 2007-2008. Apart from study VER001-8, which was a phase 3 study performed in patients with uncomplicated SSTIs, the other two studies were smaller phase 2 studies, partly including subjects with cSSTIs. Similar concerns to those expressed for the pivotal study VER001-9 with regard to the patients included with cSSTI were also expressed for these two studies. , namely that the external validity of the studied populations was not clear since the severity of the cSSTIs was uncertain, and that it was questionable whether the patients were really in need of IV antibiotic therapy. CHMP agreed nevertheless that although the clinical and microbiological outcome data from these supportive studies are in line with that of the pivotal studies, the supportive studies did not have a major impact on the assessment of efficacy of dalbavancin for the applied indication.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The rationale for the dosage regimen chosen (1000 mg on day 1 followed by 500 mg on day 8) for studies DUR001-301 and -302 was based on data from a neutropenic murine thigh infection model, a Monte Carlo simulation on PK/PD data, as well as clinical data from a phase 2 study (VER001-05) and from the earlier performed phase 3 study VER001-9. The CHMP agreed that the chosen dose regimen can be considered reasonable.

Both studies DUR001-301 and DUR001-302 were phase 3, randomised, double-blind, multicentre, double-dummy studies aiming to demonstrate non-inferior efficacy and to compare the safety of dalbavancin to a comparator regimen (vancomycin with the option to switch to oral linezolid) for the treatment of acute bacterial skin and skin structure infections known or suspected to be caused by Gram-positive bacteria. In these studies, patients with cSSTI such as major cutaneous abscess, surgical site or traumatic wound infection, or cellulitis, and at least one clinical systemic sign of infection, were included, in accordance with the definition of acute bacterial skin and skin structure infections.

Patients were randomly assigned to receive in a 1:1 ratio either two IV doses of dalbavancin (one on Day 1 and one on Day 8) or 10 to 14 days of IV vancomycin/oral linezolid. A total of 20 to 28 doses of vancomycin/linezolid, either active or placebo depending on randomization group, were to be administered. Following at least 72 hours of study drug treatment, patients could have been switched from q12h IV study drug (either dalbavancin and placebo or vancomycin and placebo) to oral therapy for patients in the vancomycin/linezolid treatment group or matching placebo for patients in the dalbavancin treatment group if clinical signs of infection had improved.

The applicant received CHMP Scientific Advice regarding the inclusion criteria of the pivotal studies. To reduce the risk of including non-severe infections, CHMP recommended that a considerable proportion of subjects should meet at least 2 SIRS criteria and that patients should be considered to require a period of 7 days of IV therapy. In addition, CHMP advised the company to include a sufficient number of patients with co-morbidities such as diabetes mellitus, peripheral vascular disorders, concomitant bacteraemia, and that the number of signs of systemic infection required for enrolment should be increased. The applicant, however, decided to include patients based on at least one sign of systemic infection and a minimum of 3 days of IV therapy for both studies. It has been clarified that a sufficiently large portion of the patients included in the pivotal studies had severe infections.

The applicant envisaged that dalbavancin would be primarily used in the treatment of MRSA. In accordance with the scientific advice received, the studies were therefore performed in regions where a high prevalence of MRSA would be expected. Despite this, less than 30% of the patients in the pivotal studies were diagnosed with infections caused by MRSA. Nevertheless, the CHMP agreed that the frequency of MRSA was not lower than what had been accepted earlier in similar marketing authorisation applications of medicinal products for the same indication.

Vancomycin is a suitable comparator for cSSTI due to MRSA but not considered as effective in treating cSSTI due to MSSA or streptococci. In those cases where cSSTI is caused by MSSA semisynthetic penicillins would be a more appropriate choice. Therefore vancomycin/linezolid might not be an ideal comparator in this setting considering the rather low number of MRSA infected patients included in the pivotal studies. CHMP agreed however that the chosen comparator could be considered acceptable since the pivotal studies were performed in

areas with an expected high prevalence of MRSA. Furthermore, the high response rates in the control arm are noted.

The primary objective for the analysis to be presented to the CHMP was to show non-inferiority in the rate of clinical success at EOT of dalbavancin compared to the comparator regimen vancomycin/linezolid. This strategy of aiming to demonstrate non-inferiority towards an appropriate reference regimen is in line with the recommendations of the CHMP guideline and was considered acceptable.

The primary outcome of the pivotal trials was the clinical status (success or failure) in the CE-EOT population at the EOT Visit (study day 14-15). The criteria for clinical success (decrease in erythema, temperature, tenderness, swelling/induration and purulent drainage) were in line with what had been accepted for similar applications. According to the CHMP guideline, clinical response (i.e. success or failure) at Test of Cure (TOC) should be the primary efficacy endpoint. In this application, the TOC visit corresponds to the End of Treatment (EOT) visit, i.e. at study day 14-15. Considering the long terminal half-life (approx. 16 days) of dalbavancin the timing of EOT is not considered optimal, since therapeutic levels of dalbavancin would still be present in the blood at EOT. However, this timing was agreed upon in the CHMP Scientific Advice, but it was considered that the consistency in outcome of the additional endpoint, clinical success at short-term follow-up (SFU) visit (day 28 +/-2 days) would be crucial. Therapeutic levels of dalbavancin would also be present at the SFU visit (Day 28) and even at the long-term follow-up (LFU) visit (Day 70). This is based on information by the applicant that serum levels of dalbavancin would be approximately 3 mg/L at the LFU assessment. In addition, MIC90s of 0.06 mg/L for staphylococci and 0.03 – 0.06 mg/L for streptococci have been observed for dalbavancin, further confirming that therapeutic levels of dalbavancin would still be present in the body at LFU. Despite some concerns that patients receiving dalbavancin might risk relapsing at a later time point, the CHMP overall agreed that this risk seemed remote and it was therefore considered that it would not have a significant impact for the assessment. The applicant has presented two separate statistical analysis plans (SAP) for the two pivotal studies DUR001-301 and DUR001-302; one for the FDA and one for the EMA (clinical success at 48-72 hours and at test of cure, respectively). Different statistical analyses were needed because the two agencies require different primary efficacy endpoints. This approach is in accordance with the CHMP Guideline on the Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev 2) and the Addendum to this guideline (EMA/CHMP/351889/2013).

The non-inferiority margin of -10% for studies DUR001-301 and DUR001-302 was considered acceptable.

Efficacy data and additional analyses

The majority of the enrolled patients in the two pivotal studies were males, whites, had creatinine clearance ≥ 30 mL/min, an elevated BMI and fever at baseline. The proportion of patients hospitalised at study entry was around 70%.

In both studies the most common type of infection was cellulitis (approximately 50-60%) and major cutaneous abscess (< 30%). Few subjects with surgical site infections were included. The mean values for the erythema areas affected were well above 75 cm^2 for all infection types in the ITT population in both treatment groups in both studies. In order to ensure that the included infections could be defined as complicated, not only the size of the lesion area is of importance, also the depth of the soft tissue involvement is a critical parameter. Regarding the local signs of infection, these were classified as severe in the majority of patients in DUR001-301. In DUR001-302 the percentage of patients with moderate signs of local infection were similar to the percentage with severe local signs. It therefore seems that the local signs of infection might be of lesser severity in this study compared to the patients in DUR001-301.

For both studies the results show that almost all patients had one systemic sign of infection (fever, WBC > 12,000 cells/mm3 or bands > 10%) in both treatment groups. In DUR001-301 around 60% met the SIRS criteria (both treatment groups) while this was the case for approx. 40% in DUR001-302. The proportion of patients classified as having a severe infection is in line or exceeds that agreed by CHMP in other recent studies used for the approval of medicinal products for cSSTI.

A high rate of success was observed in both treatment arms in DUR001-301, i.e. 87.0% of patients in the dalbavancin arm versus 91.4% of patients in the vancomycin/linezolid arm. Compared to study DUR001-301 an even higher success rate was found in DUR001-302, i.e. clinical success was 93.5% and 92.7% in the dalbavancin arm and vancomycin/linezolid arm, respectively. Non-inferiority of dalbavancin compared to vancomycin/linezolid for the primary end point clinical success at EOT in the CE population was demonstrated in studies DUR001-301 and DUR001-302. The lower limit of the 95% CI was within -10%, although a tendency to lower success rate was noticed in study 301. The outcome in the ITT population was well in line of that of the CE population.

The majority of patients had IV treatment for 72 hours or longer.

The most commonly isolated pathogen in the three pivotal studies was *Staphylococcus aureus*, of which a various part consisted of MRSA (range 65-81%), followed by *Streptococcus pyogenes*. Notably, the number of *S. pyogenes* was low in particular in study DUR001-301 and VER-001-9. A rather low proportion of cultures positive for *Streptococcus pyogenes* can be expected in cSSTI. The frequency of MRSA was relatively low, but this was deemed to be acceptable by the CHMP. The patients in the two studies had mainly monomicrobial infections. However, in DUR001-301 more patients in the dalbavancin group had monomicrobial infections when compared both to the vancomycin/linezolid group and to each of the two treatment groups in DUR001-302. This could potentially favour the result of the dalbavancin arm in DUR001-301.

Clinical success rates in patients with *S. aureus* (regardless of methicillin resistance) and streptococcal ABSSSIwere approximately 90% in both treatment groups, which is considered in line with the expected outcome as per previously conducted cSSTI studies.

Clinical success rates at EOT were similar in the dalbavancin and vancomycin/linezolid groups for all infection types. The numerically highest response rate was generally demonstrated for major abscesses, regardless of treatment. There were some imbalances within each of the two studies regarding clinical success rates in the CE-population in patients who met SIRS criteria, at SFU, but looking at the pooled data, the outcome was deemed reassuring.

In study VER001-9, the outcome for the primary endpoint (clinical cure at TOC) demonstrated non-inferiority to linezolid, with a treatment difference of -2.2% (95% CI -7.28, 2.86). Due to an imbalance of indeterminate response in the ITT population, the study was also analysed when indeterminate response were excluded, as a post-hoc analysis, and the observed treatment difference was -2.20 (95% CI -6.7, 2.3). Nevertheless., the fact that excluding all indeterminates gave results which were more similar to the CE population was not unexpected. Median time to switch to oral therapy was 2 days, which seems to be a relatively short time, further indicating that a substantial part of the patients were not seriously ill.

In general, the analyses of the secondary outcomes for DUR001-301 and DUR001-302, i.e., clinical success at EOT in the ITT population, clinical success at SFU in the ITT and CE-SFU populations, microbiological success at EOT, eradication rates for individual pathogens and clinical efficacy by individual pathogens in the microITT and ME populations, supported the results observed in the primary efficacy analysis. This was also the case with the additional outcomes, i.e., clinical success at EOT, SFU and LFU based on the investigator's assessment and early clinical response at 48-72 hours in the ITT population.

There is no concern on efficacy in the subset of patients with bacteraemia associated to ABSSSI. The number of bacteraemic cases and the clinical outcome is deemed sufficient to omit a cautionary statement in section 4.4 of the SmPC regarding the numbers of cases of bacteraemia that have been treated.

2.5.4. Conclusions on the clinical efficacy

The study populations included in the new pivotal trials DUR001-301 and DUR001-302 are judged to be clinically relevant and representative for the applied indication. It is concluded that non-inferiority vs. the comparator has been sufficiently demonstrated.

2.6. Clinical safety

Patient exposure

The safety of dalbavancin has been evaluated in 12 phase 1 studies (8 studies in healthy subjects, 4 studies in special populations), 2 phase 2 studies and 5 phase 3 studies. The clinical safety population consisted of all subjects who received any amount of study drug (defined as dalbavancin, comparator, or placebo). The program consisted of a total of 3442 subjects (3431 adults +11 adolescents), 2092 of whom were treated with dalbavancin and 1350 of whom were treated with a comparator (1276 active comparator and 74 placebo).

For the 3 double-blind phase 3 studies, VER001-9, DUR001-301 and DUR001-302, safety parameters were monitored on treatment, at the end of treatment (EOT) and at test of cure (TOC). For study VER001-9, EOT occurred on day 14-17 And TOC in study VER001-9 occurred on day 28 .For the studies DUR001-301 and DUR001-302, EOT was scheduled on day 14-15 and SFU on day 28 and LFU on day 70.

Adverse events

In the integrated phase 1 studies, the incidences of subjects with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to discontinuation of study drug were higher in the total dalbavancin group compared to the comparator group and similar between the 3 dalbavancin dose groups (<500, 500-1000, and >1000 mg).

In the phase 2/3 integrated analysis set, fewer subjects treated with dalbavancin experienced at least 1 TEAE, treatment-related TEAEs, and treatment-related SAEs than in the comparator group. The incidence of subjects experiencing TEAEs and SAEs leading to discontinuation of study drug, were similar between the total dalbavancin and total comparator treatment groups (see table below).

Table 22 Overview of Treatment-Emergent Adverse Events: Phase 2/3 Integrated Analysis Set

Number (%) of subjects with at least 1:	Dalbavancin			Total Comparator (N=1224)
	Dalbavancin 1 dose (N=338)	Dalbavancin 2 doses (N=1440)	Total Dalbavancin (N=1778)	
TEAE	124 (36.7)	675 (46.9)	**799 (44.9)**	**573 (46.8)**
P value[a]			*0.012*	
mild	96 (28.4)	552 (38.3)	**648 (36.4)**	**447 (36.5)**
moderate	51 (15.1)	289 (20.1)	**340 (19.1)**	**275 (22.5)**
severe	19 (5.6)	79 (5.5)	**98 (5.5)**	**63 (5.1)**
Tx-related AE	48 (14.2)	280 (19.4)	**328 (18.4)**	**246 (20.1)**
P value[a]			*0.014*	
possibly related	41 (12.1)	246 (17.1)	**287 (16.1)**	**214 (17.5)**
probably related	9 (2.7)	50 (3.5)	**59 (3.3)**	**57 (4.7)**
SAE	20 (5.9)	89 (6.2)	**109 (6.1)**	**80 (6.5)**
P value[a]			*0.266*	
Tx-related SAE	0	3 (0.2)	**3 (0.2)**	**9 (0.7)**
P value[a]			*0.021*	
AE leading to discontinuation of study drug	13 (3.8)	40 (2.8)	**53 (3.0)**	**35 (2.9)**
P value[a]			*0.857*	
AE leading to withdrawal from study	6 (1.8)	11 (0.8)	**17 (1.0)**	**6 (0.5)**
P value[a]			*0.434*	

TEAEs reported for dalbavancin occurred in a majority (62.9%) of the study subjects in the phase 1 integrated analysis set vs. 29.5 % in the comparator group (59.0% were given placebo, the remaining subjects were administered a single dose of 400 mg moxifloxacin). The most common AEs include headache, infusion site pain, nausea, diarrhoea and respiratory tract infection, the latter probably not related to the drug.

Table 23 Treatment Emergent Adverse Events Occurring in >2.0% of Total Dalbavancin Subjects: Phase 1 Integrated Analysis Set

AE Preferred Term	Dalbavancin n (%)				Comparator (N=122)
	Dalbavancin <500 mg (N=29)	Dalbavancin 500 - 1000 mg (N=165)	Dalbavancin >1000 mg (N=92)	Total Dalbavancin (N=286)	
Subjects with at least 1 TEAE	21 (72.4)	106 (64.2)	53 (57.6)	**180 (62.9)**	**36 (29.5)**
Headache	7 (24.1)	13 (7.9)	4 (4.3)	**24 (8.4)**	**7 (5.7)**
Infusion site pain	0	10 (6.1)	11 (12.0)	**21 (7.3)**	**1 (0.8)**
Nausea	3 (10.3)	10 (6.1)	3 (3.3)	**16 (5.6)**	**3 (2.5)**
Diarrhoea	1 (3.4)	6 (3.6)	6 (6.5)	**13 (4.5)**	**1 (0.8)**
Upper respiratory tract infection	2 (6.9)	8 (4.8)	3 (3.3)	**13 (4.5)**	**1 (0.8)**
Dizziness	0	11 (6.7)	1 (1.1)	**12 (4.2)**	**1 (0.8)**
Oropharyngeal pain	2 (6.9)	6 (3.6)	3 (3.3)	**11 (3.8)**	**2 (1.6)**
Pyrexia	6 (20.7)	4 (2.4)	1 (1.1)	**11 (3.8)**	**2 (1.6)**
Body temperature increased	0	5 (3.0)	5 (5.4)	**10 (3.5)**	**3 (2.5)**
Back pain	2 (6.9)	6 (3.6)	1 (1.1)	**9 (3.1)**	**1 (0.8)**
Cough	1 (3.4)	6 (3.6)	1 (1.1)	**8 (2.8)**	**0**
Vomiting	1 (3.4)	5 (3.0)	2 (2.2)	**8 (2.8)**	**1 (0.8)**
Fatigue	0	1 (0.6)	5 (5.4)	**6 (2.1)**	**2 (1.6)**
Infusion site erythema	0	4 (2.4)	2 (2.2)	**6 (2.1)**	**2 (1.6)**
Nasal congestion	2 (6.9)	4 (2.4)	0	**6 (2.1)**	**1 (0.8)**

Source: Table 4.8-1.

Note: Subjects are only counted once at each level of summarization. Comparator arm includes 72 placebo subjects and 50 moxifloxacin subjects.

Abbreviations: AE=adverse event, TEAE= treatment emergent adverse event.

In the phase 2/3 analysis set, the number of subjects with at least 1 TEAE among dalbavancin-treated subjects (44.9%) was slightly lower than that of comparator-treated subjects (46.8%), Table 21. The proportion of subjects with at least 1 *treatment-related* TEAE was lower among dalbavancin-treated subjects (18.4%) than that of comparator-treated subjects (20.1%). The system organ class (SOC) most commonly affected by TEAEs was gastrointestinal disorders, where 15.5% of dalbavancin-treated subjects and 16.5% of comparator-treated subjects experienced TEAEs of this SOC.

Nausea, diarrhoea and headache were the most common AEs related to the use of dalbavancin, occurring in 2.8%, 2.5% and 1.5% of the subjects, respectively.

There seem to be systematically lower incidences of almost all observed events (TEASs, SAEs, withdrawals, deaths) in the phase 3 DUR001-301/302 Integrated analysis set compared to phase 2/3 integrated analysis set. There is also a trend towards lower incidences of AEs in the dalbavancin treatment arm compared to comparator within each integrated data set. The applicant has discussed the possible reasons for the observed differences in the reported AE frequencies, and suggests that the observed difference in the overall incidence of adverse events between clinical studies may include varying practices of reporting adverse events in individual geographic regions and indications studied in each group. However, the incidence was approximately similar between the treatment arms within the sets.

Table 24 Treatment-Emergent Adverse Events Reported in >2% of the Subjects in Any Treatment Group: Phase 2/3 Integrated Analysis Set

	Dalbavancin n (%)			Comparator n (%)		
AE Preferred Term	1 Dose (N=338)	2 Doses (N=1440)	Total (N=1778)	7 Days (N=218)	14 Days (N=1006)	Total (N=1224)
Subjects with at least 1 AE	124 (36.7)	675 (46.9)	**799 (44.9)**	97 (44.5)	476 (47.3)	**573 (46.8)**
Nausea	17 (5.0)	81 (5.6)	**98 (5.5)**	15 (6.9)	63 (6.3)	**78 (6.4)**
Headache	11 (3.3)	72 (5.0)	**83 (4.7)**	8 (3.7)	51 (5.1)	**59 (4.8)**
Diarrhoea	18 (5.3)	61 (4.2)	**79 (4.4)**	10 (4.6)	62 (6.2)	**72 (5.9)**
Constipation	2 (0.6)	50 (3.5)	**52 (2.9)**	2 (0.9)	28 (2.8)	**30 (2.5)**
Vomiting	6 (1.8)	44 (3.1)	**50 (2.8)**	7 (3.2)	30 (3.0)	**37 (3.0)**
Rash	6 (1.8)	32 (2.2)	**38 (2.1)**	6 (2.8)	16 (1.6)	**22 (1.8)**
Urinary tract infection	4 (1.2)	32 (2.2)	**36 (2.0)**	2 (0.9)	14 (1.4)	**16 (1.3)**
Anaemia	4 (1.2)	30 (2.1)	**34 (1.9)**	3 (1.4)	17 (1.7)	**20 (1.6)**
Pruritus	6 (1.8)	26 (1.8)	**32 (1.8)**	7 (3.2)	28 (2.8)	**35 (2.9)**
Gamma-glutamyltransferase increased	1 (0.3)	30 (2.1)	**31 (1.7)**	2 (0.9)	17 (1.7)	**19 (1.6)**
Insomnia	2 (0.6)	25 (1.7)	**27 (1.5)**	5 (2.3)	25 (2.5)	**30 (2.5)**
Abdominal pain	3 (0.9)	21 (1.5)	**24 (1.3)**	5 (2.3)	6 (0.6)	**11 (0.9)**
Cellulitis	1 (0.3)	22 (1.5)	**23 (1.3)**	5 (2.3)	13 (1.3)	**18 (1.5)**
Dyspnoea	3 (0.9)	20 (1.4)	**23 (1.3)**	6 (2.8)	8 (0.8)	**14 (1.1)**

Source: Table 4.8-2.1.1

Notes: Version 14.0 of MedDRA was used to code adverse events. Subject assignment to Dalbavancin 1 dose or Dalbavancin 2 doses is based on actual treatment and randomized treatment regimen for studies VER001-5, VER001-9, VER001-16 (for subjects with cSSSI). For Study VER001-4, all subjects are assigned to Dalbavancin 2 doses. For studies VER001-8 and VER001-16 (subjects with uSSSI), subject assignment to Dalbavancin 1 dose or Dalbavancin 2 doses is based on true exposure. For all studies, subject assignment to Comparator 7 days or Comparator 14 days is based on true exposure. Subjects are only counted once at each level of summarization. Adverse events are presented in decreasing frequency of preferred term for the total dalbavancin arm.

Abbreviations: AE=adverse event

Adverse events of specific interest

Renal adverse events

In the phase 2/3 integrated analysis set, the frequency of renal AEs and *treatment-related* renal and urinary AEs was similar between subjects treated with dalbavancin (1.9% and 0.2%, respectively) and subjects treated with a comparator (2.0% and 0.4%, respectively).

Of the 16 cases of renal failure (PTs of acute pre-renal failure, renal failure, and acute renal failure), none of the 6 cases in dalbavancin-treated subjects were considered by the investigator to be related to treatment, and 3 (0.2%) of the 10 cases in comparator-treated subjects were considered by the investigator to be possibly or probably related to treatment.

The frequency of *serious* renal and urinary disorder AEs was similar between subjects treated with dalbavancin (0.2%) and subjects treated with a comparator (0.5%). Serious renal disorder AEs in subjects treated with dalbavancin included hydronephrosis, nephrolithiasis, renal failure, and renal failure acute, each of which

occurred in 0.1% of subjects. None of the serious renal disorder AEs in subjects treated with dalbavancin were considered related to treatment.

When subjects were categorized by baseline CrCl, the percent of subjects with at least 1 AE was similar amongst the 3 groups categorized by baseline creatinine clearance. The percent of subjects with at least 1 AE in the renal and urinary disorders SOC was higher in subjects with a baseline CrCl below 60 mL/min (3.5%) compared with subjects with a baseline value of 60-89 (2.0%) and ≥90 mL/min (1.1%).

Auditory and vestibular effects

Audiology was evaluated in the 6 phase 1 studies (VER 001-1,-2,-3,-10,-12,-13) where audiology was part of the studies. In the dalbavancin development program, a total of 105 phase 1 subjects dosed with dalbavancin have undergone stringent audiologic testing according to the applicant.

A careful review of the audiology results for VER001-3, VER001-10, VER001-12 and VER001-13, which included subjects > 65 years of age and patients with renal impairment (mild and moderate RI), did not find the results to be suggestive of any pattern of ototoxic change associated with dalbavancin.

In the phase 2/3 set, 6 dalbavancin-treated subjects (0.4%), experienced vertigo (3 subjects), tinnitus (2) and hypoacusis (1), whereas one (0.1%) in the comparator group reported a hearing adverse event. 2 events of tinnitus and 1 of vertigo were considered possibly related to the study drug (all dalbavancin). A few patients experience dizziness events that possibly were related to dalbavancin treatment. None of the cases of dizziness (related and unrelated cases) in the dalbavancin treatment group were associated with hearing impairment.

Overall, there seems to be no pattern of ototoxic change associated with dalbavancin at the proposed dosing regimen. However, dalbavancin is chemically related to the glycopeptides teicoplanin and vancomycin which both are associated with nephrotoxicity and ototoxicity, thus, a potential ototoxicity effect cannot be excluded after prolonged treatment and repeated treatment of dalbavancin.

Hepatobiliary disorders

The frequency of individual hepatobiliary AEs in the phase 2/3 set was similar between subjects treated with dalbavancin (0.1-1.7%) and subjects treated with a comparator (0.1-1.6%). The frequency of hepatobiliary AEs was comparable between subjects who received 1 dose or 2 doses of dalbavancin.

The frequency of *treatment-related* AEs in the hepatobiliary disorders SOC was similar between subjects treated with dalbavancin (0.3%) and subjects treated with a comparator (0.1%). The frequency of *serious* hepatobiliary disorder AEs was similar between subjects treated with dalbavancin and subjects treated with a comparator (0.2% in each group). None of the serious hepatobiliary disorder AEs were considered related to treatment and none had an outcome of death.

Adverse events potentially related to haematology effects

The AEs related to haematology effects are summarized for the phase 2/3 subjects in the following table. Dalbavancin seems to be associated with anaemia to the same extent as the drugs in the comparator regimens (including the myelosuppressive agent linezolid), 1.9% vs. 1.6%. The corresponding figures for *treatment-related* anaemia were 0.3% vs. 0% respectively. The frequency of anaemia was comparable between subjects who received 1 dose or 2 doses of dalbavancin.

Table 25 Adverse Events Potentially Related to Myelosuppression: Phase 2/3 Integrated Analysis Set [Number (%) of Subjects]

Number (%) of subjects with at least one AE	Dalbavancin			Comparator		
	1 dose (N=338)	2 doses (N=1440)	Total (N=1778)	7 days (N=218)	14 days (N=1006)	Total (N=1224)
Blood and lymphatic system disorders						
Anaemia NOS	4 (1.2)	30 (2.1)	**34 (1.9)**	3 (1.4)	17 (1.7)	**20 (1.6)**
Leukopenia NOS	0	7 (0.5)	**7 (0.4)**	1 (0.5)	6 (0.6)	**7 (0.6)**
Neutropenia	0	5 (0.3)	**5 (0.3)**	0	1 (0.1)	**1 (0.1)**
Thrombocytopenia	0	3 (0.2)	**3 (0.2)**	1 (0.5)	7 (0.7)	**8 (0.7)**
Pancytopenia	0	1 (0.1)	**1 (0.1)**	0	1 (0.1)	**1 (0.1)**
Investigations						
Haemoglobin decreased	0	3 (0.2)	**3 (0.2)**	0	0	**0**
Haematocrit decreased	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Platelet count decreased	1 (0.3)	1 (0.1)	**2 (0.1)**	0	1 (0.1)	**1 (0.1)**
Red blood cell count decreased	0	2 (0.1)	**2 (0.1)**	0	1 (0.1)	**1 (0.1)**
Monocyte count decreased	0	0	**0**	0	1 (0.1)	**1 (0.1)**
Congenital, familial and genetic disorders						
Sickle cell anaemia with crisis	0	2 (0.1)	**2 (0.1)**	0	0	**0**

Source: Table 4.2.1-2.1.1.

Note: Subject assignment to Dalbavancin 1 dose or Dalbavancin 2 doses is based on actual treatment and randomized treatment regimen for studies VER001-5, VER001-9, VER001-16 (for subjects with cSSSI). For Study VER001-4, all subjects are assigned to Dalbavancin 2 doses. For studies VER001-8 and VER001-16 (subjects with uSSSI), subject assignment to Dalbavancin 1 dose or Dalbavancin 2 doses is based on true exposure. For all studies, subject assignment to Comparator 7 days or Comparator 14 days is based on true exposure. AEs are presented in decreasing frequency of preferred term for the total dalbavancin arm.

Abbreviations: NOS= not otherwise specified

Cardiac safety

Results from a thorough QT trial (TQT), study DUR001-102 was provided. Study DUR001-102 was a single-centre, randomized, single-dose, placebo- and positive controlled, partially double-blind, parallel-group ECG study on 198 subjects. The results of the adequately designed and conducted thorough QT study on 99 healthy subjects given a therapeutic (1000 mg) or supratherapeutic (1500 mg) dose of dalbavancin (99 subjects received placebo or moxifloxacin), indicate that dalbavancin does not prolong the QTc interval and the drug had no effect on the heart rate, PR or QRS interval.

The ECG results of the phase 2/3 integrated analysis set demonstrated that dalbavancin does not exhibit any impact on heart rate, PR or QRS interval.

Serious adverse event / deaths / other significant events

Deaths

No subject died during the phase 1 clinical studies. All together during the phase 2/3 studies, 10 dalbavancin-treated subjects (of 1778 patients) and 15 comparator-treated (of 1224 patients) subjects died. All of the 10 deaths that occurred in the dalbavancin arms in the phase 2/3 set and were all considered as unrelated or unlikely related to the drug.

Serious adverse events

The proportion of subjects experiencing SAEs was low and similar in the dalbavancin and comparator groups in the phase 1 set (1.4% vs. 0%) and the phase 2/3 (6.1% vs. 6.5%) set (see following table). There were no severe AEs that were related to the dalbavancin treatment in the phase 1 set.

Three of 1778 patients (0.2%) treated with dalbavancin and 9/1224 (0.7%) patients treated with a comparator agent were reported to have treatment-related SAEs in the Phase 2/3 integrated analysis set.

The proportions of dalbavancin-treated subjects and comparator-treated subjects who had at least 1 SAE that led to discontinuation of study drug were similar, 1.2% vs. 1.1%.

Cellulitis, experienced by 4 (0.2%) dalbavancin-treated subjects and 2 (0.2%) comparator-treated subjects, was the most frequently occurring SAE that led to discontinuation of study drug for subjects in the phase 2/3 set. Necrotising fasciitis and subcutaneous abscess were SAEs that led to discontinuation of study drug for 2 (0.1%) dalbavancin-treated subjects each; no comparator-treated subject experienced necrotizing fasciitis or subcutaneous abscess leading to discontinuation of study drug. These SAE's may also be considered therapeutic failure.

Table 26 Serious Adverse Events by Decreasing Frequency in the Total Dalbavancin Arm (Occurring in ≥2 Dalbavancin-Treated Subjects): Phase 2/3 Integrated Analysis Set

	Dalbavancin n (%)			Comparator n (%)		
AE Preferred Term	1 Dose (N=338)	2 Doses (N=1440)	Total (N=1778)	7 Days (N=218)	14 Days (N=1006)	Total (N=1224)
Number (%) of subjects with at least 1 SAE	20 (5.9)	89 (6.2)	109 (6.1)	28 (12.8)	52 (5.2)	80 (6.5)
Cellulitis	1 (0.3)	14 (1.0)	15 (0.8)	5 (2.3)	2 (0.2)	7 (0.6)
Cardiac failure congestive	1 (0.3)	3 (0.2)	4 (0.2)	1 (0.5)	1 (0.1)	2 (0.2)
Abscess limb	1 (0.3)	2 (0.1)	3 (0.2)	1 (0.5)	0	1 (0.1)
Asthma	1 (0.3)	2 (0.1)	3 (0.2)	0	0	0
Atrial fibrillation	1 (0.3)	2 (0.1)	3 (0.2)	0	1 (0.1)	1 (0.1)
Osteomyelitis	0	3 (0.2)	3 (0.2)	1 (0.5)	2 (0.2)	3 (0.2)
Anal abscess	0	2 (0.1)	2 (0.1)	0	1 (0.1)	1 (0.1)
Arthritis bacterial	0	2 (0.1)	2 (0.1)	0	0	0
Bacteraemia	0	2 (0.1)	2 (0.1)	0	1 (0.1)	1 (0.1)
Cardio-respiratory arrest	0	2 (0.1)	2 (0.1)	0	0	0
Cardiopulmonary failure	1 (0.3)	1 (0.1)	2 (0.1)	1 (0.5)	1 (0.1)	2 (0.2)
Deep vein thrombosis	0	2 (0.1)	2 (0.1)	0	2 (0.2)	2 (0.2)
Febrile neutropenia	0	2 (0.1)	2 (0.1)	0	0	0
Gastrointestinal haemorrhage	1 (0.3)	1 (0.1)	2 (0.1)	1 (0.5)	1 (0.1)	2 (0.2)
Impaired healing	0	2 (0.1)	2 (0.1)	0	1 (0.1)	1 (0.1)
Leukopenia	0	2 (0.1)	2 (0.1)	0	0	0
Myocardial infarction	0	2 (0.1)	2 (0.1)	0	0	0
Necrotising fasciitis	1 (0.3)	1 (0.1)	2 (0.1)	0	1 (0.1)	1 (0.1)
Peripheral ischaemia	0	2 (0.1)	2 (0.1)	0	0	0
Pneumonia	1 (0.3)	1 (0.1)	2 (0.1)	1 (0.5)	1 (0.1)	2 (0.2)
Pyrexia	0	2 (0.1)	2 (0.1)	0	1 (0.1)	1 (0.1)
Respiratory failure	0	2 (0.1)	2 (0.1)	0	0	0
Subcutaneous abscess	1 (0.3)	1 (0.1)	2 (0.1)	0	0	0

A total of 10 treatment-related SAEs were experienced in 3 (0.2%) subjects treated with dalbavancin and 9 (0.7%) subjects treated with comparator (see following table). Except for acute renal failure (reported in 2 comparator-treated subjects), all treatment-related SAEs were reported in 1 subject each.

Table 27 Treatment-Related Serious Adverse Events by Decreasing Frequency in the Total Dalbavancin Group: Phase 2/3 Integrated Analysis Set

AE Preferred Term	Dalbavancin n (%)			Comparator n (%)		
	1 Dose (N=338)	2 Doses (N=1440)	Total (N=1778)	7 Days (N=218)	14 Days (N=1006)	Total (N=1224)
Number (%) of subjects with at least 1 Tx-related TEAE	0	3 (0.2)	**3 (0.2)**	4 (1.8)	5 (0.5)	**9 (0.7)**
Anaphylactoid reaction	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Cellulitis	0	1 (0.1)	**1 (0.1)**	1 (0.5)	0	**1 (0.1)**
Leukopenia	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Face oedema	0	0	**0**	0	1 (0.1)	**1 (0.1)**
Gastrointestinal disorder	0	0	**0**	0	1 (0.1)	**1 (0.1)**
Nephropathy toxic	0	0	**0**	0	1 (0.1)	**1 (0.1)**
Pancreatitis acute	0	0	**0**	1 (0.5)	0	**1 (0.1)**
Pancytopenia	0	0	**0**	0	1 (0.1)	**1 (0.1)**
Renal failure acute	0	0	**0**	2 (0.9)	0	**2 (0.2)**
Thrombocytopenia	0	0	**0**	0	1 (0.1)	**1 (0.1)**

Source: Table 4.4.2-2.1.

*In addition to the 1 case of treatment-related leukopenia presented in Source Table 4.4.2-2.1, other subject treated with 2 doses of dalbavancin (Subject VER001-09-0038-0040) had leukopenia had leukopenia assessed by the investigator as unrelated, but probably related by the Sponsor."

Laboratory findings

The median values, along with the total number of patients available at each assessment for important clinical laboratory parameters in the Phase 2/3 integrated safety database are presented at each sampling time-point in the following table. No significant difference in any of the clinical laboratory values was observed between treatment groups at any time point.

Table 28 Clinical laboratory parameters: Phase 2/3 integrated safety database

Clinical Laboratory Parameter	Treatment	Category	Baseline	On-treatment	Day 14	Day 28
		Min, Max	0, 5	0, 4	0, 4	0, 3
	Comparator	N	1205	982	1087	486
		Median	0.8	0.8	0.9	0.9
		Min, Max	0, 5	0, 5	0, 5	0, 3
Haemoglobin (g/dL)	Dalbavancin	N	1731	1328	1544	949
		Median	13.4	13	13.4	13.6
		Min, Max	0, 19	0, 19	5, 19	7, 18
	Comparator	N	1196	955	1064	489
		Median	13.3	12.9	13.3	13.5
		Min, Max	5, 19	5, 18	6, 29	6, 18
Neutrophils	Dalbavancin	N	589	538	530	5
		Median	7.2	4.9	4.3	3.1
		Min, Max	2, 27	0, 28	1, 16	1, 5
	Comparator	N	591	525	538	4
		Median	7.3	4.8	4.1	5.3
		Min, Max	1, 31	1, 23	1, 26	4, 7
Platelets ($10^3/\mu L$)	Dalbavancin	N	1705	1294	1520	945
		Median	252	282	293.5	255
		Min, Max	14, 820	17, 1548	25, 1147	7, 958
	Comparator	N	1180	940	1051	488
		Median	248	263	274	272
		Min, Max	25, 992	20, 1191	45, 894	56, 842
Urea Nitrogen (mg/dL)	Dalbavancin	N	1752	1350	1566	952
		Median	13	13	14	14
		Min, Max	2, 89	2, 73	1, 87	3, 83
	Comparator	N	1202	979	1084	484
		Median	14	12	14	14
		Min, Max	3, 86	3, 94	2, 89	4, 76
WBC ($10^3/\mu L$)	Dalbavancin	N	1730	1312	1538	949
		Median	9.7	7.6	7.2	7
		Min, Max	0, 42	0, 31	0, 29	0, 31
	Comparator	N	1194	945	1059	489
		Median	9.8	7.4	6.9	7.3
		Min, Max	1, 35	0, 27	1, 29	2, 99

Clinical Laboratory Parameter	Treatment	Category	Baseline	On-treatment	Day 14	Day 28
ALT (units/L)	Dalbavancin	N	1676	1319	1542	948
		Median	23	27	25	25
		Min, Max	0, 1402	5, 383	3, 622	6, 953
	Comparator	N	1173	967	1065	474
		Median	22	24	25	25
		Min, Max	1, 402	3, 473	4, 592	5, 413
AST (units/L)	Dalbavancin	N	1668	1302	1532	949
		Median	22	24	23	23
		Min, Max	0, 956	8, 315	2, 289	5, 716
	Comparator	N	1161	952	1059	474
		Median	22	23	23	22
		Min, Max	0, 257	5, 354	6, 274	2, 479
Alk. Phos. (units/L)	Dalbavancin	N	1704	1337	1558	940
		Median	81	78	78	79
		Min, Max	17, 597	0, 543	18, 505	16, 482
	Comparator	N	1179	973	1076	476
		Median	81	76	79	80
		Min, Max	15, 891	21, 654	14, 527	21, 507
Creatinine (mg/dL)	Dalbavancin	N	1754	1353	1569	956
		Median	0.9	0.8	0.9	0.9

Haematology

The incidences of subjects with potentially clinically significant (PCS) hematology values that were also potentially clinically significant changes (PCSC) were similar between treatment groups in the phase 1 integrated analysis set, phase 2/3 integrated analysis set, and phase 3 DUR001-301/302 integrated analysis set, see table below. At TOC, the number of tested subjects was substantially lower.

Thrombocytosis also occurred in both treatment groups (dalbavancin 0.6%) in the phase 2/3 set.

Table 29 Potentially Clinically Significant Values for Selected Hematology Parameters That Were Also Potentially Clinically Significant Changes: Phase 2/3 Integrated Analysis Set

	Dalbavancin						Comparator					
Parameter	1 dose		2 doses		Total		7 days		14 days		Total	
Timepoint	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Hemoglobin Low (≤0.8 × LLN and fold decrease ≥0.25)												
On-tx	64	0	1240	7 (0.6)	1304	7(0.5)	30	0	910	6(0.7)	940	6(0.6)
EOT	275	0	1230	7 (0.6)	1505	7(0.5)	166	1(0.6)	875	5(0.6)	1041	6(0.6)
TOC	266	2 (0.8)	652	4 (0.6)	918	6(0.7)	129	0	344	4(1.2)	473	4(0.8)
WBCs Low (≤0.5 × LLN and fold decrease ≥0.75)												
On-tx	64	0	1224	2 (0.2)	1288	2(0.2)	30	0	900	2(0.2)	930	2(0.2)
EOT	277	0	1223	1 (0.1)	1500	1(0.1)	166	0	869	1(0.1)	1035	1(0.1)
TOC	269	0	653	0	922	0	129	0	344	0	473	0
Neutrophils Low (≤0.5 × LLN and fold decrease ≥0.75)												
On-tx	59	0	1109	1 (0.1)	1168	1(0.1)	27	0	817	2(0.2)	844	2(0.2)
EOT	263	0	1092	0	1355	0	160	0	805	1(0.1)	965	1(0.1)
TOC	249	0	561	0	810	0	122	0	293	0	415	0
Platelets Low (≤0.6 × LLN and fold decrease ≥0.4)												
On-tx	63	0	1188	7 (0.6)	1251	7(0.6)	30	0	886	7(0.8)	916	7(0.8)
EOT	272	0	1195	2 (0.2)	1467	2(0.1)	158	0	860	4(0.5)	1018	4(0.4)
TOC	265	0	641	4 (0.6)	906	4(0.4)	127	0	339	1(0.3)	466	1(0.2)

LLN=lower limit of normal

Serum chemistry

Phase 2/3 integrated analysis set and Phase 3 DUR001-301/302 integrated analysis set

See table below for potentially clinically significant (PCS) values that were also potentially clinically significant changes (PCSC). Of note, at TOC the number of tested subjects was lower.

The number and percentage of subjects with PCS values that were also PCS changes for the most clinically relevant chemistry parameters (potassium, alkaline phosphatase, ALT, AST, total bilirubin, glucose, creatinine, and BUN) was similar between dalbavancin and comparator treatment groups.

Table 30 Subjects With Potentially Clinically Significant (PCS) Laboratory Results That Were Also Potentially Clinically Significant Changes (PCSC) in Laboratory Results: Phase 2/3 Integrated Analysis Set

Parameter	Dalbavancin						Comparator					
	1 dose		2 doses		Total		7 days		14 days		Total	
Timepoint	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Alkaline Phosphatase High (≥1.5 × ULN and fold increase ≥2)												
On-tx	60	0	1242	8 (0.6)	**1302**	**8 (0.6)**	30	0	912	4 (0.4)	**942**	**4 (0.4)**
EOT	267	1 (0.4)	1239	8 (0.6)	**1506**	**9 (0.6)**	165	1 (0.6)	873	5 (0.6)	**1038**	**6 (0.6)**
TOC	256	2 (0.8)	644	0	**900**	**2 (0.2)**	129	0	319	2 (0.6)	**448**	**2 (0.4)**
ALT High (≥3 × ULN and fold increase ≥3)												
On-tx	61	0	1202	6 (0.5)	**1263**	**6 (0.5)**	30	0	902	1 (0.1)	**932**	**1 (0.1)**
EOT	263	0	1203	6 (0.5)	**1466**	**6 (0.4)**	160	0	858	3 (0.3)	**1018**	**3 (0.3)**
TOC	257	3 (1.2)	636	4 (0.6)	**893**	**7 (0.8)**	126	0	318	0	**444**	**0**
AST High (≥3 × ULN and fold increase ≥3)												
On-tx	60	0	1180	8 (0.7)	**1240**	**8 (0.6)**	31	0	875	1 (0.1)	**906**	**1 (0.1)**
EOT	263	0	1186	3 (0.3)	**1449**	**3 (0.2)**	163	2 (1.2)	841	1 (0.1)	**1004**	**3 (0.3)**
TOC	257	3 (1.2)	637	2 (0.3)	**894**	**5 (0.6)**	129	0	316	3 (0.9)	**445**	**3 (0.7)**
Total Bilirubin High (≥1.5 × ULN and fold increase ≥3)												
On-tx	42	0	1208	1 (0.1)	**1250**	**1 (0.1)**	27	0	896	0	**923**	**0**
EOT	254	0	1208	2 (0.2)	**1462**	**2 (0.1)**	161	0	859	1 (0.1)	**1020**	**1 (0.1)**
TOC	246	0	618	1 (0.2)	**864**	**1 (0.1)**	125	1 (0.8)	308	0	**433**	**1 (0.2)**
Glucose High (≥3 × ULN and fold increase ≥3)												
On-tx	62	1 (1.6)	1240	3 (0.2)	**1302**	**4 (0.3)**	31	0	901	1 (0.1)	**932**	**1 (0.1)**
EOT	280	1 (0.4)	1241	2 (0.2)	**1521**	**3 (0.2)**	171	0	875	0	**1046**	**0**
TOC	271	1 (0.4)	658	2 (0.3)	**929**	**3 (0.3)**	135	0	333	0	**468**	**0**
Glucose Low (≤0.6 × LLN and fold decrease ≥0.4)												
On-tx	62	0	1240	1 (0.1)	**1302**	**1 (0.1)**	31	0	901	1 (0.1)	**932**	**1 (0.1)**
EOT	280	1 (0.4)	1241	3 (0.2)	**1521**	**4 (0.3)**	171	0	875	3 (0.3)	**1046**	**3 (0.3)**
TOC	271	0	658	0	**929**	**0**	135	0	333	0	**468**	**0**
Creatinine High (1.5 × ULN and fold increase ≥2)												
On-tx	63	0	1276	1 (0.1)	**1339**	**1 (0.1)**	31	1 (3.2)	934	1 (0.1)	**965**	**2 (0.2)**
EOT	286	0	1265	3 (0.2)	**1551**	**3 (0.2)**	175	2 (1.1)	893	4 (0.4)	**1068**	**6 (0.6)**
TOC	277	0	669	1 (0.1)	**946**	**1 (0.1)**	136	0	339	1 (0.3)	**475**	**1 (0.2)**
BUN High (≥3 × ULN and fold increase ≥3)												
On-tx	63	0	1271	0	**1334**	**0**	31	0	929	0	**960**	**0**
EOT	285	0	1261	1 (0.1)	**1546**	**1 (0.1)**	173	0	889	1 (0.1)	**1062**	**1 (0.1)**
TOC	277	0	664	0	**941**	**0**	134	0	337	0	**471**	**0**

Hepatobiliary parameters

Phase 2 / 3 integrated analysis set

Mild to moderate increase of gamma-glutamyltransferase and lactate dehydrogenase were noted in 1.7% and 1.2% of the dalbavancin-treated subjects.

The majority of subjects in both treatment groups with hepatobiliary abnormalities had elevations in ALT and AST that were >ULN to 3×ULN. Less or equal to 2% of dalbavancin-treated and comparator-treated subjects had ALT or AST abnormalities that were >3×ULN.

The frequency of subjects with very high levels (>10xULN) of aminotransferases noted post- baseline was low and similar between treatment groups (3 subjects in each treatment group). There was no evidence of altered liver function accompanying or promptly following elevation of aminotransferases such as an increase in serum total bilirubin unexplained by other causes. There were no cases of Hy's law seen in the dalbavancin clinical program.

Out of the subjects that had an ALT <ULN at baseline, ALT was still elevated in 6.0% (47/778) of the dalbavancin-treated subjects at TOC.

Safety in special populations

Gender

Females more frequently reported adverse events than males, but there were no major differences between the dalbavancin-treated group vs the comparator group of study subjects related to gender.

Age

All causality adverse events were more common among dalbavancin treated subjects ≥ 65 years of age than in the younger age group, 50.5% of subjects vs. 43.8%. But treatment-related TEAEs and treatment-related TEAEs that led to discontinuation of study drug did not differ between the 2 age groups. In the phase 2/3 integrated analysis set, gastrointestinal disorders SOC were the most commonly reported TEAEs in subjects ≥65 years of age and <65 years of age in the dalbavancin group (17.9% and 14.9%, respectively), and in the comparator group (14.8% and 16.9%, respectively).

Adverse event rates based on various age categories for dalbavancin-treated patients and comparator-treated patients in the Phase 2/3 database are presented in the tables below. As expected, the AE rate for older patients in both treatment groups is generally higher than that observed in younger patients. An exception is the observed frequency of SAE's in dalbavancin-treated subjects older than 75 years of age which is slightly lower than that observed in subjects 65 to 74 years of age, however, the number of patients in the oldest age group is small.

Table 31 Frequency of adverse events by age in dalbavancin-treated patients – Phase 2/3 integrated safety database

	Age Group			
Age in years	**Age < 65 n/N (%)**	**Age 65-74 n/N (%)**	**Age 75-84 n/N (%)**	**Age ≥ 85 n/N (%)**
Dalbavancin-treated patients	1465/1778 (82.4)	170/1778 (9.6)	130/1778 (7.3)	13/1778 (0.7)
Number of Patients Who Experienced at Least One of				
AE	656/1465 (44.8)	87/170 (51.2)	70/130 (53.8)	8/13 (61.5)
TEAE	641/1465 (43.8)	82/170 (48.2)	68/130 (52.3)	8/13 (61.5)
Serious TEAE	74/1465 (5.1)	21/170 (12.4)	14/130 (10.8)	0
Treatment-Emergent SAE Leading to Death	3/1465 (0.2)	3/170 (1.8)	4/130 (3.1)	0
Discontinuation of Study Drug due to TEAE	39/1465 (2.7)	10/170 (5.9)	2/130 (1.5)	1/13 (7.7)
AE related to falling	4/1465 (0.3)	3/170 (1.8)	2/130 (1.5)	0
Cardiovascular Events	64/1465 (4.4)	15/170 (8.8)	17/130 (13.1)	1/13 (7.7)
Cerebrovascular Events	0	0	1/130 (0.8)	0
Infections and infestations	159/1465 (10.9)	21/170 (12.4)	22/130 (16.9)	3/13 (23.1)
Nervous system disorders	126/1465 (8.6)	17/170 (10.0)	7/130 (5.4)	2/13 (15.4)

Table 32 Frequency of adverse events by age in comparator-treated patients – Phase 2/3 integrated safety database

	Age Group			
Age in years	**Age < 65 n/N (%)**	**Age 65-74 n/N (%)**	**Age 75-84 n/N (%)**	**Age ≥ 85 n/N (%)**
Comparator-treated Patients, N1	995/1224 (81.3)	126/1224 (10.3)	90/1224 (7.4)	13/1224 (1.1)
Number of Patients Who Experienced at Least One of				
AE	478/995 (48.0)	57/126 (45.2)	44/90 (48.9)	8/13 (61.5)
TEAE	465/995 (46.7)	56/126 (44.4)	44/90 (48.9)	8/13 (61.5)
Serious TEAE	54/995 (5.4)	12/126 (9.5)	11/90 (12.2)	3/13 (23.1)
Treatment-Emergent SAE Leading to Death	4/995 (0.4)	6/126 (4.8)	4/90 (4.4)	0
Discontinuation of Study Drug due to TEAE	26/995 (2.6)	3/126 (2.4)	4/90 (4.4)	2/13 (15.4)
AE related to falling	2/995 (0.2)	1/126 (0.8)	1/90 (1.1)	1/13 (7.7)
CV Events	60/995 (6.0)	12/126 (9.5)	6/90 (6.7)	0
Cerebrovascular Events	1/995 (0.1)	1/126 (0.8)	0	0
Infections and infestations	142/995 (14.3)	12/126 (9.5)	15/90 (16.7)	5/13 (38.5)
Nervous system disorders	86/995 (8.6)	4/126 (3.2)	6/90 (6.7)	3/13 (23.1)

Subjects with impaired renal function.

Phase1 integrated analysis set

There were two phase 1 studies (VER001-11 and VER001-13) that evaluated the safety of 500 mg or 1000 mg of dalbavancin in a single dose in subjects with mild (CrCl 50-79 mL/min), moderate (30-49 mL/min), or severe renal impairment (<30 mL/min) or end-stage renal disease (haemodialysis-dependent), and in healthy subjects with normal renal function (CrCl ≥80 mL/min).

28 subjects with renal impairment were included; 6 had mild, 6 had moderate and 16 had severe renal impairment or end-stage renal disease. Overall, dalbavancin was well tolerated in subjects with renal impairment.

Phase 2/3 integrated analysis set

A total of 1436 patients with different degrees of renal impairment (Dalbavancin; mild RI: N=504, moderate RI: N=310, severe RI: N=32) was enrolled in the Phase 2/3 studies.

Table 33 Overview of Treatment-Emergent Adverse Events by Creatinine Clearance Category—Phase 2/3 Integrated Analysis Set: Safety Population

	Phase 2/3 Integrated Analysis Set	
	Dalbavancin (N=1736)	Comparator (N=1197)
Number of subjects, N1		
<30 mL/min	32	21
30 to 59 mL/min	310	225
60 to 89 mL/min	504	344
≥90 mL/min	890	607
Number of subjects with ≥1 TEAE, n/N1 (%)		
<30 mL/min	15/32 (46.9)	9/21 (42.9)
30 to 59 mL/min	152/310 (49.0)	117/225 (52.0)
60 to 89 mL/min	226/504 (44.8)	162/344 (47.1)
≥90 mL/min	381/890 (42.8)	272/607 (44.8)

Source: Table 4.2.1-3.11.1
Notes: N1 = Number of subjects in each specified category
Abbreviation: TEAE = treatment-emergent adverse event

In subjects that received dalbavancin or comparator in the 30 to 59, 60 to 89, and ≥90 mL/min groups, incidences of subjects with TEAEs were similar between treatment groups. Although, due to the small sample sizes for subjects with baseline CrCl values <30 mL/min, there were insufficient data to make meaningful comparisons by baseline renal impairment that include these subjects.

Gastrointestinal disorders SOC were the most commonly reported TEAEs for subjects in the dalbavancin group with baseline CrCl values in each of the CrCl value categories and ranged from 14.3 % to 18.8 %.

Subjects with impaired hepatic function

In the phase 1 set, dalbavancin was well tolerated in 17 subjects with mild to severe hepatic impairment that were given 1000 mg on day 1 and 500 mg on day 8.

Immunological/allergic/skin-associated events

Phase 1 integrated analysis set

In the dalbavancin phase 1 set, 15 events of various skin reactions occurred including one with respiratory symptoms. Two cases were considered as possibly or probably related to dalbavancin (urticaria and facial flushing combined with respiratory symptoms) and there were another 13 events of skin reactions (e.g. rash, erythema and red man syndrome) reported to be associated with the use of the drug.

Phase 2/3 integrated analysis set

The frequency of individual AEs representing potential allergic reactions was similar between subjects treated with dalbavancin (0.1-2.1%) and subjects treated with a comparator (0.1-1.8%), see table below. Subjects who

received 2 doses of dalbavancin doses experienced slightly more allergic reactions than those who received 1 dose: 58/1440 (4.0%) vs. 11/338 (3.3%), respectively.

One event of anaphylactoid reaction occurred in a dalbavancin-treated subject. The applicant has proposed to include the following sentence in Section 4.4 "If an allergic reaction to Xydalba occurs, administration should be discontinued and appropriate therapy for the allergic reaction should be instituted" which is endorsed.

The duration of treatment-related skin rash in the dalbavancin treatment group was roughly similar (or possibly shorter) to that observed in the comparator treatment group (median: 7 days vs 7 days; mean: 5.6 days vs 9.8 days). There does not seem to be any indication of a longer duration of the skin reactions when compared to the comparator. Skin events accounted for 48% of the events that led to premature discontinuation of dalbavancin. However, the premature discontinuation rate was low as such and occurred to a similar extent in the dalbavancin and comparator groups.

Table 34 Potential Allergic Reactions: Phase 2/3 Integrated Analysis Set [Number (%) of Subjects]

Number (%) of subjects with at least 1 AE	Dalbavancin n (%)			Comparator n (%)		
	1 Dose (N=338)	2 Doses (N=1440)	Total (N=1778	7 Days (N=218)	14 Days (N=1006)	Total (N=1224)
Immune system disorders						
Hypersensitivity	1 (0.3)	4 (0.3)	**5 (0.3)**	1 (0.5)	0	**1 (0.1)**
Food allergy	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Allergic oedema	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Anaphylactoid reaction	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Seasonal allergy	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Drug hypersensitivity	0	0	**0**	0	1 (0.1)	**1 (0.1)**
Skin and subcutaneous tissue disorders						
Rash	6 (1.8)	32 (2.2)	**38 (2.1)**	6 (2.8)	16 (1.6)	**22 (1.8)**
Urticaria	3 (0.9)	5 (0.3)	**8 (0.4)**	3 (1.4)	5 (0.5)	**8 (0.7)**
Rash pruritic	0	4 (0.3)	**4 (0.2)**	1 (0.5)	2 (0.2)	**3 (0.2)**
Rash generalized	1 (0.3)	1 (0.1)	**2 (0.1)**	0	2 (0.2)	**2 (0.2)**
Rash macular	0	2 (0.1)	**2 (0.1)**	0	2 (0.2)	**2 (0.2)**
Swelling face	0	2 (0.1)	**2 (0.1)**	1 (0.5)	1 (0.1)	**2 (0.2)**
Drug rash with eosinophilia and systemic symptoms	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Rash erythematous	0	1 (0.1)	**1 (0.1)**	0	0	**0**
Rash papular	0	1 (0.1)	**1 (0.1)**	0	1 (0.1)	**1 (0.1)**
Rash maculo-papular	0	0	**0**	0	1 (0.1)	**1 (0.1)**
Red man syndrome	0	0	**0**	1 (0.5)	1 (0.1)	**2 (0.2)**

Safety related to drug-drug interactions and other interactions

The limited clinical information obtained on concomitant drug therapy during dalbavancin treatment does not indicate any important drug-drug interactions. The safety of combining dalbavancin with drugs that are nephro- or ototoxic (class-related concerns for glycopeptides) has not been fully clarified.

Discontinuation due to adverse events

The percentage of subjects who had at least 1 TEAE that resulted in discontinuation of study drug was similar between subjects treated with dalbavancin (3.0%) and subjects treated with the comparator (2.9%), see table below.

Table 35 Adverse Events Resulting in Discontinuation of Study Drug in ≥2 Subjects in any Treatment Group: Phase 2/3 Integrated Analysis Set

	Dalbavancin n (%)			Comparator n (%)		
AE Preferred Term	1 Dose (N=338)	2 Doses (N=1440)	Total (N=1778)	7 Days (N=218)	14 Days (N=1006)	Total (N=1224)
Number (%) of subjects with at least 1 AE leading to discontinuation	13 (3.8)	40 (2.8)	**53 (3.0)**	25 (11.5)	10 (1.0)	**35 (2.9)**
Cellulitis	1 (0.3)	5 (0.3)	**6 (0.3)**	2 (0.9)	0	**2 (0.2)**
Osteomyelitis	1 (0.3)	4 (0.3)	**5 (0.3)**	0	0	**0**
Rash	0	4 (0.3)	**4 (0.2)**	2 (0.9)	1 (0.1)	**3 (0.2)**
Arthritis bacterial	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Bacteraemia	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Diarrhoea	0	2 (0.1)	**2 (0.1)**	1 (0.5)	0	**1 (0.1)**
Drug eruption	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Insomnia	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Leukocytosis	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Muscle spasms	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Nausea	1 (0.3)	1 (0.1)	**2 (0.1)**	4 (1.8)	1 (0.1)	**5 (0.4)**
Necrotising fasciitis	1 (0.3)	1 (0.1)	**2 (0.1)**	0	0	**0**
Pruritus	1 (0.3)	1 (0.1)	**2 (0.1)**	2 (0.9)	0	**2 (0.2)**
Subcutaneous abscess	1 (0.3)	1 (0.1)	**2 (0.1)**	0	0	**0**
Tenosynovitis	0	2 (0.1)	**2 (0.1)**	0	0	**0**
Pneumonia	0	1 (0.1)	**1 (0.1)**	2 (0.9)	0	**2 (0.2)**
Urticaria	1 (0.3)	0	**1 (0.1)**	2 (0.9)	1 (0.1)	**3 (0.2)**
Cerebrovascular accident	0	0	**0**	0	2 (0.2)	**2 (0.2)**
Dyspnoea	0	0	**0**	2 (0.9)	0	**2 (0.2)**
Erythema	0	0	**0**	2 (0.9)	0	**2 (0.2)**
Renal failure acute	0	0	**0**	2 (0.9)	1 (0.1)	**3 (0.2)**
Vomiting	0	0	**0**	2 (0.9)	0	**2 (0.2)**

2.6.1. Discussion on clinical safety

The size of the safety database for dalbavancin exceeds ICH suggestions, (1230 subjects in 3 double-blind pivotal studies on the sought indication cSSSI/ABSSSI, but also another 859 subjects in 17 Phase 1, 2 and 3 studies).

The most common adverse events occurring during dalbavancin treatment are nausea (5.5%), headache (4.7%), diarrhea (4.4%), constipation (2.9%) and vomiting (2.8%). The symptoms were of mild to moderate intensity in almost all subjects. The median duration of nausea, headache and diarrhoea was 1.0 to 2.0 days.

Three of 1778 patients (0.2%) treated with dalbavancin and 9/1224 (0.7%) patients treated with a comparator agent were reported to have treatment-related SAEs in the Phase 2/3 integrated analysis set. In the pool of the phase 2/3 studies a total of 10 deaths (0.56%) were reported in the dalbavancin-group compared with 15 deaths (1.2%) in the comparator group. All of the 10 deaths that occurred in the dalbavancin arms in the phase 2/3 set and were all considered as unrelated or unlikely related to the drug.

The frequency of individual potential allergic reactions (mainly skin events) was 0.1-2.1% for subjects treated with dalbavancin. Subjects given 2 dalbavancin doses developed slightly more allergic reactions than those administered 1 dose. One event of anaphylactoid reaction occurred in a dalbavancin-treated subject and an adequate warning has been included in SmPC section. The duration of treatment-related skin rash in the dalbavancin treatment group was roughly similar (or possibly shorter) to that observed in the comparator treatment group (median: 7 days vs 7 days; mean: 5.6 days vs 9.8 days). There does not seem to be any indication of a longer duration of the skin reactions when compared to the comparator. The premature discontinuation rate was low as such and occurred to a similar extent in the dalbavancin and comparator groups.

The hepatobiliary effects noted during dalbavancin treatment are mild to moderate elevations of the hepatic enzymes. No cases fulfilling Hy's law criteria were seen. Hepatobiliary events and elevations of ALT, AST and gamma-glytamyl transferase occur more frequently after 2 doses of dalbavancin than after 1 dose of the drug. The frequency of individual hepatobiliary AEs was for the dalbavancin group 0.1-1.7% vs. for the comparator group 0.1-1.6%, and the frequency of treatment-related hepatobiliary events was 0.3% in the dalbavancin phase 2/3 set compared to 0.1% for the comparator drugs. There were no serious liver adverse events considered to be related to dalbavancin. To conclude, the use of dalbavancin is associated with a small risk of mild to moderate hepatobiliary effects. The SmPC section is considred adequate.

Regarding potential hematology effect, a similar number of patients were reported to have an AE of anaemia in the dalbavancin (1.9 %) and comparator (1.6%) treatment groups in the phase 2/3 dataset, and the shift analysis shows that also similar frequencies of patients treated with dalbavancin had haematocrit or haemoglobin values lower than the normal range post-baseline relative to the comparator-treated group (in patients having normal values at baseline). Only one treatment-related SAE of myelosuppression was reported in the dalbavancin treatment group. This was a mild transient case of leukopenia. In addition similar frequencies in dalbavancin-treated patients had significant haemoglobin and haematocrit changes postbaseline relative to comparator-treated patients. Thus, there is no apparent evidence of myelosuppression or of anaemia associated with dalbavancin in this clinical setting and at the duration of treatment in the present clinical studies.

Three subjects had a *C. difficile* diarrhoea/colitis of moderate intensity that was considered related to dalbavancin and an adequate warning has been included in SmPC section 4.4.

The frequency of all renal and urinary events in the phase 2/3 set was similar between subjects treated with dalbavancin and the comparator group, 1.9% vs. 2.0%, and the corresponding figures for treatment-related renal and urinary events were 0.2% and 0.5% respectively. Only dysuria and pollakiuria were considered related to dalbavancin. Six events of renal failure occurred among dalbavancin-treated subjects although none of the cases are considered to be related to dalbavancin treatment. No serious renal adverse event was considered related to dalbavancin treatment.

Audiology assessment was included in a sufficient number of subjects. A careful review of the audiology results for VER001-3, VER001-10, VER001-12 and VER001-13, which included subjects > 65 years of age and patients

with renal impairment (mild and moderate RI), did not find the results to be suggestive of any pattern of ototoxic change associated with dalbavancin. In the phase 2/3 set, 6 dalbavancin-treated subjects (0.4%), experienced vertigo (3 subjects), tinnitus (2) and hypoacusis (1), whereas one (0.1%) in the comparator group reported a hearing adverse event. Two events of tinnitus and 1 of vertigo were considered possibly related to the study drug (all dalbavancin). A few patients experienced dizziness events that possibly were related to dalbavancin treatment. None of the cases of dizziness (related and unrelated cases) in the dalbavancin treatment group were associated with hearing impairment. Overall, there seems to be no pattern of ototoxic change associated with dalbavancin at the proposed dosing regimen. However, dalbavancin is chemically related to the glycopeptides teicoplanin and vancomycin which both are associated with nephrotoxicity and ototoxicity, thus, a potential ototoxicity effect can not be excluded after prolonged treatment and repeated treatment of dalbacancin.

Regarding drug interaction studies the limited clinical information obtained on concomitant drug therapy during dalbavancin treatment does not indicate any important drug-drug interactions. The safety of combining dalbavancin with drugs that are nephro- or ototoxic (class-related concerns for glycopeptides) has not been fully clarified.

The overall incidences of TEAEs in the subpopulations, i.e. sex, age, renal and hepatic function were analysed. There was no large difference noted in the subgroups. Although it is emphasised that only few (N=32) subjects with severe renal impairment were included which preclude any meaningful comparisons by baseline renal impairment that include these subjects.

Overall, the available safety data indicate that dalbavancin is tolerated to the same extent as the used comparator drugs, mainly linezolid, vancomycin and cefazolin. Gastrointestinal symptoms, headache and rash of mild to moderate intensity are common adverse reactions. Hematology effects and mild to moderate hepatobiliary effects are uncommon reactions, but elevations of various hepatobiliary parameters are common. However, dalbavancin is chemically related to the glycopeptides teicoplanin and vancomycin. The adverse effect profile of dalbavancin is similar to these drugs with 2 important exceptions: vancomycin and teicoplanin are both associated with nephrotoxicity and ototoxicity; dalbavancin on the other hand, has not clearly been associated with such toxicities. In clinical practice, a need for prolonged treatment and repeated treatment of dalbavancin can be foreseen, thus there is a potential risk for off-label use.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of dalbavancin is as expected for a glycopeptide antibiotic. There was no apparent safety issues for which dalbavancin were markedly worse than the comparators. The available clinical safety data of dalbavancin indicate that the safety profile of dalbavancin in the applied indication of cSSTI may be considered acceptable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.0 is acceptable. The PRAC advice is attached.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Emergence of resistance Pseudomembranous colitis Hypersensitivity
Important potential risks	Hepatic disorder Otovestibular toxicity Nephrotoxicity Haematologic effects Off-Label Use
Missing information	Use in immunocompromised patients Use in patients with moderate and severe hepatic impairment Use in patients with a CrCl<30 ml/min receiving haemodialysis Paediatric use Use in pregnant and lactating women

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
In vitro susceptibility surveillance studies with dalbavancin will be performed (surveillance programmes) Category 3	To monitor for the post marketing occurrence of resistance to dalbavancin, including resistance patterns and trends.	To monitor for the post marketing occurrence of resistance to dalbavancin, including resistance patterns and trends.	Planned	Yearly reports supplied by laboratories conducting surveillance activities which the Applicant will submit to Health Authorities.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Emergence of resistance	SmPC wording Section 4.4: "**Non-susceptible organisms** The use of antibiotics may promote the overgrowth of non-susceptible micro-organisms. If superinfection occurs during therapy, appropriate measures should be taken." Section 5.1: "**Mechanism of resistance** All Gram-negative bacteria are inherently resistant to dalbavancin. Resistance to dalbavancin in Staphylococcus spp. and Enterococcus spp. is mediated by VanA, a genotype that results in modification of the target peptide in nascent cell wall. Based on *in vitro* studies the activity of dalbavancin is not affected by other classes of vancomycin resistance genes. Dalbavancin MICs are higher for vancomycin-intermediate staphylococci (VISA) than for fully vancomycin susceptible strains. If the isolates with higher dalbavancin MICs represent stable phenotypes and are correlated with resistance to the other glycopeptides, then the likely mechanism would be an increase in the number of glycopeptide targets in nascent peptidoglycan. Cross-resistance between dalbavancin and other classes of antibiotics was not seen in *in vitro* studies. Methicillin resistance has no impact on dalbavancin activity."	None proposed
Pseudomembranous colitis	SmPC wording Section 4.4: "***Clostridium difficile*-associated diarrhoea** Antibacterial-associated colitis and pseudomembranous colitis have been reported with the use of nearly all antibiotics and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the treatment with dalbavancin (see section 4.8). In such circumstance, the discontinuation of dalbavancin and the use of supportive measures together with the administration of specific treatment for *Clostridium difficile* should be considered. These patients must never be treated with medicinal products that suppress the peristalsis." Section 4.8: "SOC Infections and Infestations: Uncommon: *Clostridium difficile* colitis"	None proposed
Hypersensitivity	SmPC wording Section 4.3: "Hypersensitivity to the active substance or to any of the excipients listed in section 6.1" Section 4.4: "**Hypersensitivity reactions** Xydalba should be administered with caution in patients known to be hypersensitive to other glycopeptides since cross-hypersensitivity may occur. If an allergic reaction to Xydalba occurs, administration should be discontinued and appropriate therapy for the allergic reaction should be instituted." Section 4.8:	None proposed

<table>
<tr><td></td><td>
<table>
<tr><th>System Organ Class</th><th>Common</th><th>Uncommon</th><th>Rare</th></tr>
<tr><td>Immune system disorders</td><td></td><td></td><td>anaphylactoid reaction</td></tr>
<tr><td>Respiratory, thoracic and mediastinal disorders</td><td></td><td></td><td>bronchospasm</td></tr>
<tr><td>Skin and subcutaneous tissue disorders</td><td>rash</td><td>pruritus, urticaria</td><td></td></tr>
</table>
</td><td></td></tr>
<tr><td>Hepatic disorder</td><td>
SmPC wording
Section 4.2:
“<u>Hepatic impairment</u>
No dosage adjustment of dalbavancin is recommended for patients with mild hepatic impairment (Child Pugh A). Caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic impairment (Child Pugh B & C) as no data are available to determine appropriate dosing (see sections 5.2).”
Section 5.2:
“<u>Hepatic impairment</u>
The pharmacokinetics of dalbavancin were evaluated in 17 subjects with mild, moderate, or severe hepatic impairment and compared to 9 matched healthy subjects with normal hepatic function. The mean AUC was unchanged in subjects with mild hepatic impairment compared to subjects with normal hepatic function; however, the mean AUC decreased by 28 % and 31 %, respectively, in subjects with moderate and severe hepatic impairment. The cause and the clinical significance of the decreased exposure in subjects with moderate and severe hepatic function are unknown. For dosing instructions in subjects with hepatic impairment refer to section 4.2.”
Section 4.8:
“In Phase 2/3 clinical studies, 1778 patients received dalbavancin. The most common adverse reactions occurring in ≥1% of patients treated with dalbavancin were … increased gamma-glutamyl transferase (1.1%) … and were generally of mild or moderate severity.”
<table>
<tr><th>System Organ Class</th><th>Common</th><th>Uncommon</th></tr>
<tr><td>Investigations</td><td>gamma-glutamyl transferase increased</td><td>blood lactate dehydrogenase increased, alanine aminotransferase increased, aspartate aminotransferase increased, liver function test abnormal, transaminases increased, blood alkaline phosphatase increased, hepatic enzyme increased</td></tr>
</table>
Section 5.3:
“Dalbavancin toxicity has been evaluated after daily intravenous administration for durations of up to 3 months in rats and dogs. Dose-dependent toxicity included serum chemistry and histological evidence of … hepatic injury…”
</td><td>None proposed</td></tr>
<tr><td>Otovestibular toxicity</td><td>
SmPC wording
Section 4.8:
“Ototoxicity has been associated with glycopeptide use (vancomycin and teicoplanin); patients who are receiving concomitant therapy with an ototoxic agent, such as an
</td><td>None proposed</td></tr>
</table>

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<tr><td></td><td>aminoglycoside, may be at increased risk.”</td><td></td></tr>
<tr><td>Nephrotoxicity</td><td>SmPC wording
Section 4.4:
“<u>Renal impairment</u>
Information on the efficacy and safety of dalbavancin in patients with creatinine clearance < 30 ml/min is limited. Based on simulations, dose adjustment is needed for patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regular haemodialysis (see sections 4.2 and 5.2).”
Section 4.2:
“<u>Renal impairment</u>
Dose adjustments are not required for patients with mild or moderate renal impairment (creatinine clearance ≥ 30 to 79 ml/min). Dose adjustments are not required for patients receiving regularly scheduled haemodialysis (3 times/week), and dalbavancin may be administered without regard to the timing of haemodialysis.
In patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regularly scheduled haemodialysis, the recommended once-weekly dose regimen for dalbavancin should be reduced to 750 mg followed one week later by 375 mg (see section 5.2).”
Section 5.2:
“<u>Renal impairment</u>
The pharmacokinetics of dalbavancin were evaluated in 28 subjects with varying degrees of renal impairment and in 15 matched control subjects with normal renal function. Following a single dose of 500 mg or 1000 mg dalbavancin, the mean plasma clearance (CL_T) was reduced 11 %, 35 %, and 47 % in subjects with mild (CL_{CR} 50 - 79 ml/min), moderate (CL_{CR} 30 – 49 ml/min), and severe (CL_{CR} < 30 ml/min) renal impairment, respectively, compared to subjects with normal renal function. The mean AUC for subjects with creatinine clearance < 30 ml/min was approximately 2 - fold higher. The clinical significance of the decrease in mean plasma CL_T, and the associated increase in AUC0-∞ noted in these pharmacokinetic studies of dalbavancin in subjects with severe renal impairment has not been established. Dalbavancin pharmacokinetics in subjects with end-stage renal disease receiving regularly scheduled renal dialysis (3 times/week) were similar to those observed in subjects with mild to moderate renal impairment, and less than 6 % of an administered dose is removed after 3 hours of haemodialysis. For dosing instructions in subjects with renal impairment refer to section 4.2.”
Section 5.3:
“Dalbavancin toxicity has been evaluated after daily intravenous administration for durations of up to 3 months in rats and dogs. Dose-dependent toxicity included serum chemistry and histological evidence of renal … injury…”</td><td>None proposed</td></tr>
<tr><td>Haematologic effects</td><td>SmPC wording
Section 4.8 tabulated list of adverse reactions:
<table><tr><td>System Organ Class</td><td>Common</td><td>Uncommon</td></tr><tr><td>Blood and lymphatic system disorders</td><td></td><td>anaemia, thrombocytosis, eosinophilia, leucopenia, neutropenia</td></tr><tr><td>Investigations</td><td></td><td>platelet count increased</td></tr></table></td><td>None proposed</td></tr>
<tr><td>Off-label use</td><td>SmPC wording
Section 4.1:
“Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (see sections 4.4 and 5.1).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.”
Section 4.2:</td><td>None proposed</td></tr>
</table>

	"**Recommended dosage and duration of treatment for adults** The recommended once-weekly dosage regimen for dalbavancin in adult patients with ABSSSI is 1000 mg followed one week later by 500 mg (see sections 5.1 and 5.2)." "**Paediatric population** The safety and efficacy of dalbavancin in children aged from birth to <18 years has not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made. " Section 4.4: "**Limitations of the clinical data** There is limited data on safety and efficacy of dalbavancin when administered for more than two doses (one week apart). In ABSSSI the types of infections treated were confined to cellulitis/erysipelas, abscesses and wound infections only. The efficacy of dalbavancin has not been established in other types of ABSSSI. There is no experience with dalbavancin in the treatment of severely immunocompromised patients." Section 5.1: "Clinical efficacy against specific pathogens Efficacy has been demonstrated in clinical studies against the pathogens listed for ABSSSI that were susceptible to dalbavancin *in vitro:* • *Staphylococcus aureus,* • *Streptococcus pyogenes,* • *Streptococcus agalactiae,* • *Streptococcus dysgalactiae,* • *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius,* and *S. constel*latus). Antibacterial activity against other relevant pathogens Clinical efficacy has not been established against the following pathogens although *in vitro* studies suggest that they would be susceptible to dalbavancin in the absence of acquired mechanisms of resistance: • Group G streptococci • *Clostridium perfringens,* • *Peptostreptococcus spp*."	
Use in immunocompromised patients	SmPC wording Section 4.4 : "**Limitations of the clinical data** There is no experience with dalbavancin in the treatment of severely immunocompromised patients."	None proposed
Use in patients with moderate and severe hepatic impairment	SmPC wording Section 4.2: "**Hepatic Impairment** Caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic impairment (Child Pugh B & C) as no data are available to determine appropriate dosing (see section 5.2)." Section 5.2: "**Hepatic impairment** The pharmacokinetics of dalbavancin were evaluated in 17 subjects with mild, moderate, or severe hepatic impairment and compared to 9 matched healthy subjects with normal hepatic function. The mean AUC was unchanged in subjects with mild hepatic impairment compared to subjects with normal hepatic function; however, the mean AUC decreased by 28 % and 31 %, respectively, in subjects with moderate and severe hepatic impairment. The cause and the	None proposed

	clinical significance of the decreased exposure in subjects with moderate and severe hepatic function are unknown. For dosing instructions in subjects with hepatic impairment refer to section 4.2."	
Use in patients with a CrCl<30 ml/min receiving haemodialysis	SmPC wording Section 4.2: "**Renal impairment** In patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regularly scheduled haemodialysis, the recommended once-weekly dose regimen for dalbavancin should be reduced to 750 mg followed one week later by 375 mg (see section 5.2)." Section 4.4: "**Renal impairment** Information on the efficacy and safety of dalbavancin in patients with creatinine clearance < 30 ml/min is limited. Based on simulations, dose adjustment is needed for patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regular haemodialysis (see sections 4.2 and 5.2)." Section 5.2: "**Renal impairment** The pharmacokinetics of dalbavancin were evaluated in 28 subjects with varying degrees of renal impairment and in 15 matched control subjects with normal renal function. Following a single dose of 500 mg or 1000 mg dalbavancin, the mean plasma clearance (CL_T) was reduced 11 %, 35 %, and 47 % in subjects with mild (CL_{CR} 50 - 79 ml/min), moderate (CL_{CR} 30 – 49 ml/min), and severe (CL_{CR} < 30 ml/min) renal impairment, respectively, compared to subjects with normal renal function. The mean AUC for subjects with creatinine clearance < 30 ml/min was approximately 2 - fold higher. The clinical significance of the decrease in mean plasma CL_T, and the associated increase in AUC0-∞ noted in these pharmacokinetic studies of dalbavancin in subjects with severe renal impairment has not been established. Dalbavancin pharmacokinetics in subjects with end-stage renal disease receiving regularly scheduled renal dialysis (3 times/week) were similar to those observed in subjects with mild to moderate renal impairment, and less than 6 % of an administered dose is removed after 3 hours of haemodialysis. For dosing instructions in subjects with renal impairment refer to section 4.2."	None proposed
Paediatric use	SmPC wording Section 4.2: "**Paediatric population** The safety and efficacy of dalbavancin in children aged from birth to <18 years has not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made." Section 5.1: "**Paediatric population** The European Medicines Agency has deferred the obligation to submit results of studies with Xydalba in one or more of the subsets of the paediatric population in ABSSSI (see section 4.2 and 5.2 for information on paediatric use)." Section 5.2: "**Paediatric population** The safety and efficacy of Xydalba in children aged from birth to < 18 years have not yet been established. A total of 10 paediatric patients with ages 12 to 16 years who had resolving infections were given single doses of either dalbavancin 1000 mg (body weight ≥ 60 kg) or dalbavancin 15 mg/kg (body weight < 60 kg). Mean plasma exposures for dalbavancin, based on AUCinf (17,495 µg•h/ml and 16,248 µg •h/ml) and C_{max} (212 µg/ml and 191 µg/ml) were similar when administered as 1000 mg to paediatric subjects (12 - 16 years) weighing > 60 kg (61.9 - 105.2 kg) or as 15 mg/kg to paediatric subjects weighing < 60 kg (47.9 - 58.9 kg). Apparent terminal t½ was similar for	None proposed

	dalbavancin doses of 1000 mg and 15 mg/kg, with mean values of 227 and 202 hours, respectively. The safety profile of dalbavancin in the subjects aged between 12 and 16 years in this study was consistent with the safety profile observed in adults treated with dalbavancin."	
Use in pregnant and lactating women	SmPC wording Section 4.6: "**Pregnancy** There are no data from the use of dalbavancin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Xydalba is not recommended during pregnancy unless clearly necessary. **Breast-feeding** It is unknown whether dalbavancin is excreted in human milk. However, dalbavancin is excreted in the milk of lactating rats and may be excreted in human breast milk. Dalbavancin is not well absorbed orally; however an impact on the gastrointestinal flora or mouth flora of a breast-feeding infant cannot be excluded. A decision must be made whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Xydalba taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Fertility** Studies in animals have shown reduced fertility (see section 5.3). The potential risk for humans is unknown." Section 5.3: "Reproductive toxicity studies in rats and rabbits showed no evidence of a teratogenic effect. In rats, at exposures approximately 3 times above clinical exposure, there was reduced fertility and an increased incidence of embryo-lethality, reductions in foetal weight and skeletal ossification and increased neonatal mortality. In rabbits abortion occurred in conjunction with maternal toxicity at exposures below the human therapeutic range."	None proposed

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Dalbavancin is a second generation semi-synthetic lipoglycopeptide antibiotic structurally related to teicoplanin. Its mechanism of action, like that of other glycopeptides, involves the interruption of cell wall synthesis which results in bacterial cell death. Dalbavancin is active against important groups of Gram-positive bacteria, including strains of methicillin resistant *Staphylococcus aureus* (MRSA) and some *S. aureus* with reduced

susceptibility to glycopeptides (GISA), as well as pathogenic streptococci. 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 (IV) dosing. Dalbavancin is administered as an initial 1000-mg dose, followed by a 500-mg dose one week later. This might be an advantage for the patients compared to other antibiotics used for treating the same infection type and which have to be injected more frequently (typically every 12th or 24th hour). Dosages should be adjusted for renal insufficiency.

The efficacy of dalbavancin for the targeted treatment indication cSSTI was evaluated in 3 phase 3 studies (DUR001-301, DUR001-302, and VER001-9). Patients with infections consistent with cSSTI, defined as infections involving deeper soft tissue or requiring significant surgical intervention, were eligible for enrolment into the 3 pivotal studies.

A sufficiently large proportion of patients enrolled in the two recent pivotal studies had severe infections as judged by SIRS criteria. Non-inferiority of dalbavancin compared to vancomycin/linezolid for the primary end point, clinical success at EOT in the CE population, was demonstrated in study DUR001-301 (87.0% versus 91.4%) and DUR001-302 (93.5% versus 92.7%). The lower limit of the 95% CI was well within -10%, although a tendency to lower success rate was noticed in study DUR001-301. The outcome in the ITT population was well in line of that of the CE population. Consistency in secondary endpoints, clinical response at 48-72 hours post-study drug initiation in the ITT population; study DUR001-301 (83.3% versus 81.8%) and DUR001-302 (76.8% versus 78.3%), as well as for clinical success at SFU (day 28) in the CE population; study DUR001-301 (93.8% versus 96.1%) and DUR001-302 (96.3% versus 94.5%), for dalbavancin and vancomycin/linezolid, respectively.

In study VER001-9 the outcome for the primary endpoint clinical cure at TOC demonstrated non-inferiority to linezolid. Primary endpoint clinical response rate at TOC in the CE population (88.9% versus 91.2%, respectively, treatment difference -2.2, 95%CI -7.28, 2.86).

In the phase 3 studies DUR001-301 and -302, the most common categories of infection were cellulitis (52% to 55%) in contrast to study VER001-9 where little less than 30% were categorized as cellulitis. In that study there was a category of deep soft tissue infection (approximately 16%). Major cutaneous abscess constituted 23.6% to 30.2% in the two more recent studies, similar as in the older study, which is in line with current EU guidance. Further, the Addendum to the antibacterial guideline states that patients should demonstrate a protocol-defined minimum number of signs and symptoms associated with an ongoing acute infectious process, which was generally fulfilled for the patients included in these two more recently performed studies.

The CHMP agreed to a change of the wording of the proposed indication from “treatment of complicated skin and soft tissue infections (cSSTI)” to “treatment of acute bacterial skin and skin structure infections (ABSSSI)” that describes better the patient population enrolled in the pivotal trials, namely that the types of infections treated were confined to cellulitis/erysipelas, abscesses and wound infections.

The most commonly isolated pathogen in the three phase 3 studies was *Staphylococcus aureus*, of which a various part consisted of MRSA (range 65-81%), followed by *Streptococcus pyogenes*. The by-pathogen microbial response data from the phase 3 studies indicate non-inferiority to the comparators in key species, as supported by *in vitro* microbiology data.

Clinical success rates at EOT were similar in the dalbavancin and vancomycin/linezolid groups for all infection types. The numerically highest response rate was generally demonstrated for major abscesses, regardless of treatment.

There was no indication on differences in clinical outcome between treatment groups in respect of baseline demographic characteristics such as age, gender, race or ethnicity, severity of illness, presence of bacteraemia or by a history of diabetes mellitus. Also, the number of bacteraemic cases and the associated clinical outcome

are deemed sufficient to omit a cautionary statement in section 4.4 of the SmPC regarding the numbers of cases of bacteraemia that have been treated.

Uncertainty in the knowledge about the beneficial effects.

Efficacy data of dalbavancin beyond two weeks treatment is limited. Also, there is no experience with dalbavancin in the treatment of severely immunocompromised patients.

Risks

Unfavourable effects

Overall, the safety profile of dalbavancin is as expected for a glycopeptide antibiotic. There were no apparent safety issues for which dalbavancin was markedly worse compared to comparators.

The most frequent unfavourable effects associated with dalbavancin are nausea, diarrhoea and headache. These adverse reactions were of mild to moderate intensity, the median duration was 2 days, and they were therefore not considered to be of considerable clinical importance.

The most important unfavourable effects associated with the use of dalbavancin are skin-associated reactions (0.1-1%) which occurred to a similar extent in the comparator group. Subjects given two dalbavancin doses developed slightly more allergic reactions than those administered one dose. The duration of treatment-related skin rash in the dalbavancin treatment group was roughly similar (or possibly shorter) than that observed in the comparator treatment group. The premature discontinuation rate was low as such and occurred to a similar extent in the dalbavancin and comparator groups. One event of anaphylactoid reaction occurred in a dalbavancin-treated subject and as a result an adequate warning has been included in the SmPC.

The use of dalbavancin is associated with a small risk of mild to moderate hepatobiliary effects. There is no apparent evidence of myelosuppression or of anaemia associated with dalbavancin in this clinical setting and at the duration of treatment in the present clinical studies. Relevant information is included in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Renal adverse effects are considered important potential unfavourable effects, because dalbavancin belongs to the group of nephro-and ototoxic glycopeptides.

The frequency of all renal and urinary events in the phase 2/3 set was similar between subjects treated with dalbavancin and the comparator group, 1.9% vs. 2.0%, and the corresponding figures for treatment-related renal and urinary events were 0.2% and 0.5% respectively. Only dysuria and pollakiuria were considered related to dalbavancin. No serious renal adverse event was considered related to dalbavancin treatment. Although it is emphasised that only few (N=32) subjects with severe renal impairment were included which preclude any meaningful comparisons by baseline renal impairment that include these subjects.

Significant auditory effects have not been detected in the clinical trials, but are considered as important potential unfavourable effects, because dalbavancin belongs to the group of nephro-and ototoxic glycopeptides. Even though there seems to be no pattern of ototoxic change associated with dalbavancin at the proposed dosing

regimen, a potential ototoxicity effect cannot be excluded after prolonged treatment and repeated treatment of dalbavancin.

In clinical practice, a need for prolonged treatment and repeated treatment of dalbavancin can be foreseen, thus there is a potential risk for off-label use. There is limited data on dalbavancin dosed to steady state and, available data show that weekly administrations (for up to eight weeks) do not result in dramatically elevated maximum concentrations through accumulation.

There is a concern regarding development of resistance in bacterial isolates due to long half-life of dalbavancin. The results from studies performed hitherto indicate however that there is possibly low probability of selection for glycopeptide resistance.

Benefit-risk balance

Importance of favourable and unfavourable effects

In the era of escalating antimicrobial resistance world-wide, leading to an increasing number of patients that cannot be successfully treated for severe infections, there is a clear need of new antibacterial agents targeting multi-drug resistant pathogens. Methicillin-resistant staphylococci (MRSA and MRSE) as well as staphylococci with decreased susceptibility to currently available glycopeptides cause a real clinical threat in many settings. Dalbavancin seems to have the potential to add an alternative treatment option to other glycopeptides and oxazolidinones, in terms of increased potency to certain resistance phenotypes and possibly by an improved safety profile. The characteristics of dalbavancin of once weekly dosage, may be convenient in clinical practice, but also a disadvantage from a safety perspective in case of toxic reactions. It might also pose concerns in regards to development of resistance in bacterial isolates and a potential risk of relapse in the longer term.

The populations included in the two pivotal studies are considered to be representative for the target population.

The adverse effect profile of dalbavancin is similar to those of other glycopeptides, with important exceptions: vancomycin and teicoplanin are both associated with nephrotoxicity and ototoxicity; dalbavancin on the other hand, has not clearly been associated with such toxicities at the proposed dose regimen. However, in clinical practice, the occurrence of repeated treatment with dalbavancin cannot be excluded, necessitating the need to further monitor this.

Benefit-risk balance

The CHMP agreed that the overall benefit-risk balance of Xydalba is positive.

Discussion on the benefit-risk balance

Dalbavancin is considered to be a valuable addition to available treatment alternatives considering the potential extended activity against glycopeptides intermediate susceptible staphylococci (GISA) along with a more convenient dosage regimen of Xydalba compared to older glycopeptides. The safety characteristics are sufficiently well characterised.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xydalba in the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that

dalbavancin hydrochloride is qualified as a new active substance.