RISK MANAGEMENT PLAN - EU

Xydalba (dalbavancin)

RMP version to be assessed as part of this application:

RMP version number	7.1
Data Lock Point (DLP)	21/Jun/2021
Date of final sign off	01/Aug/2022
Qualified Person for Pharmacovigilance (QPPV) name Deputy QPPV name	Sina Schader, EU QPPV QPPV oversight declaration: The content of the RMP has been reviewed and approved by the marketing authorization holder QPPV through an electronic document system per company standard operating procedure.
Contact person for this RMP	[redacted]

Rationale for submitting an updated RMP

RMP Version	Rationale
7.1	This RMP has been updated due to the following: • To correct a discrepancy in Table 37 stating that there have been 14 serious postmarketing cases of emergence of resistance • To provide the discussion about 2 adverse events of otovestibular toxicity that were documented for Phase 1 Study DUR001-106

Summary of significant changes in this RMP:

RMP Version	Significant changes in the RMP
7.1	Correction of postmarketing, Emergence of Resistance cases in Table 37. Discussion of 2 adverse events of otovestibular toxicity as an Important Potential Risk in Table 37.

Other RMP versions under evaluation:

RMP Version	Rationale
7.0	This RMP has been updated to include data from paediatric trials (completed and ongoing) required as per the Paediatric Investigation Plan agreed with EMA.

Details of the currently approved RMP:

RMP version number	6.0
Date of approval (opinion date):	17/Feb/2020
Approved with procedure	EMEA/H/C/002840/R/0028 CP no: EMEA/H/C/002840

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES AND SUBTABLES

ABBREVIATIONS

ABI	Ankle brachial index
ABSSSI	Acute bacterial skin and skin structure infections
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BID	Twice daily
BUN	Blood urea nitrogen
CA	Community-acquired
CA-MRSA	Community-acquired MRSA
CD	Cluster of differentiation
CDAD	C. Difficile associated diarrhoea
CDC	Centers for Disease Control
CI	Confidence interval
CL_T	mean plasma clearance
CRBSI	Catheter-related bloodstream infections
CrCl	Creatinine clearance
cSSTI	Complicated skin and soft tissue infections
EEA	European economic area
EMA/EMEA	European Medicines Agency
EOT	End of Treatment
ESRD	End-stage renal disease
EU	European union
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GISA	Glycopeptide-intermediate S. Aureus
HA-MRSA	Hospital-acquired MRSA
hGISA	Heterogeneous GISA
HIV	Human immunodeficiency virus
HLT	High level term
ICD	International Classification of Diseases
ICU	Intensive care unit

ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MIC	Minimal inhibitory concentration
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-sensitive S. Aureus
NA	Not applicable
NHANES	National Health and Nutrition Examination Survey
NHDS	National hospital discharge survey
NICU	Neonatal Intensive Care Units
NNIS	National nosocomial infection surveillance
NOAEL	No-observed adverse effect level
NOEL	No-observed effect level
OR	Odds ratio
PAD	Peripheral arterial disease
PIP	Paediatric investigational plan
PK	Pharmacokinetic
PL	Package leaflet
PMARP	Per Million of Age-Related Population
PSUR	Periodic safety update report
PT	Preferred Term (of MedDRA)
RBC	Red blood cells
RMP	Risk management plan
RR	Relative risk
SAE	Serious adverse event
SIRS	Systemic inflammatory response syndrome
SJS	Stevens–Johnson syndrome
SmPC	Summary of Product Characteristic
SMQ	Standardised MedDRA Query
SOC	System Organ Class (of MedDRA)
SSHAIP	Scottish Surveillance of Healthcare Associated Infection Programme
ßhCG	ß human Chorionic Gonadotrophin
SSI	Surgical site infections
SSTI	Skin and soft tissue infections
TEAE	Treatment emergent adverse event

TEN	Toxic epidermal necrolysis
TOC	Test of cure
TSN	The surveillance network
U.S.	United states
ULN	Upper limit of normal
uSSTI	Uncomplicated skin and soft tissue infections
VISA	Vancomycin intermediate *S. aureus*
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin resistant *S. aureus*
WBC	White blood cell

PART I: PRODUCT OVERVIEW

Table 1- Product Overview

Active substance(s) (INN or common name)	Dalbavancin
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical (ATC) Code)	Antibacterials for systemic use, glycopeptide antibacterials, ATC Code: J01XA04
Medicinal products to which this RMP refers	1

Table 2- Xydalba

Invented name(s) in the European Economic Area (EEA)	Xydalba
Authorisation procedure	Centralised
Brief description of the product including:	
• chemical class	Dalbavancin, is a bactericidal lipoglycopeptide active against susceptible strains of Gram-positive bacteria.
• summary of mode of action	Its mechanism of action involves interruption of cell wall synthesis by binding to the terminal D-alanyl-D-alanine of the stem peptide in nascent cell wall peptidoglycan, preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits resulting in bacterial cell death.
• important information about its composition	Not applicable.
Indication(s) in the EEA	Current: Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

	Proposed: Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients aged 3 months and older. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Posology and route of administration in the EEA	Current: *Recommended dose and duration of treatment for adults* The recommended dose of dalbavancin in adult patients with ABSSSI is 1500 mg administered as either a single infusion of 1500 mg or as 1000 mg followed one week later by 500 mg. *Elderly* No dose adjustment is necessary. *Renal impairment* 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 dose is reduced to either 1000 mg administered as a single infusion or 750 mg followed one week later by 375 mg. *Hepatic impairment* No dose 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. *Paediatric population* The safety and efficacy of dalbavancin in children aged from birth to <18 years has not yet been established. <u>Method of administration</u> *Intravenous use* Xydalba must be reconstituted and then further diluted prior to administration by intravenous infusion over a 30 - minute period. For

	instructions on reconstitution and dilution of the medicinal product before administration, see Section 6.6 of the SmPC. Proposed: *Adults* The recommended dose of dalbavancin in adult patients with ABSSSI with creatinine clearance of 30 ml/min and above is 1500 mg administered as either a single infusion of 1500 mg or as 1000 mg followed one week later by 500 mg. *Paediatric population* The recommended dose of dalbavancin in paediatric patients with ABSSSI with creatinine clearance of 30 ml/min/1.73m^2 and above is a single-dose regimen based on the age and weight of the paediatric patient, administered as a single infusion. <u>Children and adolescents aged from 6 years to less than 18 years:</u> The recommended dose of dalbavancin in paediatric patients aged from 6 years to less than 18 years is a single dose of 18 mg/kg (maximum 1,500 mg). <u>Infants and children aged from 3 months to less than 6 years:</u> The recommended dose of dalbavancin in paediatric patients aged from 3 months to less than 6 years is a single dose of 22.5 mg/kg (maximum 1,500 mg). <u>Special Populations</u> *Elderly* No dose adjustment is necessary. *Renal impairment* Dose adjustments are not required for adult patients with mild or moderate renal impairment (creatinine clearance ≥30 to 79 ml/min). Dose adjustments are not required for adult patients receiving regularly scheduled haemodialysis (3 times/week), and dalbavancin may be administered without regard to the timing of haemodialysis. In adult patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regularly scheduled haemodialysis, the recommended dose is reduced to either 1000 mg administered as a single infusion or 750 mg followed one week later by 375 mg. There is insufficient information to recommend dosage adjustment for patients younger than 18 years with creatinine clearance less than 30 ml/min/1.73m^2.

	Hepatic impairment No dose 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. *Paediatric population* The safety and efficacy of dalbavancin in children aged < 3 months old have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.
Pharmaceutical form(s) and strengths Current	Powder for concentrate for solution for infusion (powder for concentrate). White to off-white to pale yellow powder. Each vial contains dalbavancin hydrochloride equivalent to 500 mg dalbavancin. After reconstitution each ml contains 20 mg dalbavancin. The diluted solution for infusion must have a final concentration of 1 to 5 mg/ml dalbavancin.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

SI.1 Indication

Current:
Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Proposed:
Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients aged 3 months and older.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

SI.1.1 Incidence

Table 3- Incidence

Incidence of target indication	Acute bacterial skin and skin structure infections (ABSSSI) or skin and soft tissue infections (SSTI) are among the most common infections seen in the community and the hospital. ABSSSI can range in severity from uncomplicated infection, such as simple folliculitis, to complicated infection involving deeper soft tissue (Fung et al, 2003). Data on the incidence of ABSSSI are lacking, as most of these infections are secondary to either a hospitalisation (e.g., surgery) or underlying disease (e.g., diabetes mellitus). No population-based studies of the diagnosed incidence of ABSSSI have been published; most studies focus on just one condition (e.g., surgical site infections, diabetic foot ulcers) or a specific pathogen. While the exact incidence of ABSSSI is unknown, it has been reported that an increase in the incidence of SSTI overall has been observed as a result of a number of risk factors, such as aging of the general population, an increase in the number of critically ill patients, a higher incidence of immunocompromised patients (e.g., those with HIV infection, cancer patients receiving chemotherapy, organ transplant recipients), and the recent emergence of multidrug resistant pathogens (Raghavan and Linden, 2004). Surgical Site Infections Surgical site infections (SSI) are among the most frequent nosocomial infections. The incidence of SSI varies by surgical procedure, patient risk factors, and perioperative conditions. Rates of SSI are often based on nosocomial infection surveillance surveys, which may underestimate the rate as infection may occur after hospital discharge. It has been reported that SSI become evident within 21 days and most (between 12% and 84%) are detected after patients are discharged from the hospital. (Smyth and Emmerson, 2000) Between 1986 and 1996, the National Nosocomial Infection Surveillance (NNIS) system reported that of 593,344 operations, 15,523 (2.6%) were complicated by SSI. Of these SSI, two-thirds were incisional and one-third were organ/space infections. A five-year (1995-2000) prospective cohort study at a veteran hospital in the United States (U.S.) found the incidence of SSI was 3.2% among noncardiac surgical patients. (Malone et al, 2002) In France (1999-2004), the incidence of SSI overall was 1.68% when patients were followed for a median of 28 days; SSI incidence varied from 1.2% for herniorrhaphy to 9.2% for colon surgery. (Olivier et al, 2006) In Scotland (2002-2006), the incidence of in-patient SSI was 1.5% (95% CI, 1.4-1.6) of reported surgical procedures. (SSHAIP, 2007) Over a 6-year period (1997- 2003), 5457 infections resulted from 149,745 surgical procedures in English hospitals, ranging from 2.2% for total hip replacements to 14.9% for limb amputation. (NINSS, 2004)

	<u>*Staphylococcus aureus*</u> The annual incidence of invasive *S. aureus* soft tissue infections in western Sweden was 9.2 per 100,000 persons. More than half of these infections (53%) were community-acquired, with approximately one fourth each related to nosocomial or health-care (nursing home or home health-care) infections. (Jacobsson et al, 2007) *Paediatric patients* ABSSSI are a significant source of morbidity in children as well as adults; cutaneous abscesses and cellulitis are the predominant types of skin infections evaluated by paediatricians (Mistry 2013). <u>Surgical site infection</u> A prospective cohort of children who received a procedure at a tertiary care academic hospital in Italy reported an SSI incidence of 1.0 per 100 procedures after 30 days follow-up (Ciofi 2017).

SI.1.2 Prevalence

Table 4- Prevalence

Prevalence of target indication	Similarly, the prevalence of ABSSSI is difficult to track. Prevalence data generally come from surveillance studies of nosocomial infections within the hospital setting. Nosocomial infections including SSI represent a significant source of ABSSSI. *Nosocomial Skin and Soft Tissue Infections* In 1992 study among ICUs in 17 countries in Western Europe reported 5% for nosocomial infections were skin and soft tissue infections. (Vincent et al, 1995) Similarly in 2001, in 15 Italian hospitals the point prevalence of skin and soft tissue infections was 5.6% of all nosocomial infections. (NINSS, 2004) A higher rate was reported in general academic and public French hospitals. A 1996 study reported that 11% of nosocomial infections were skin and soft tissue infections with almost one-third occurring in patients in long-term or rehabilitation wards. (The French Prevalence Survey Study Group, 2000) *Cellulitis* Based on the 2004 U.S. National Hospital Discharge Survey (NHDS), the prevalence of cellulitis and abscess as a first-listed discharge diagnosis was 19.2 per 10,000 persons. (Kozak et al, 2006) Based on 1991-1992 Morbidity Statistics from General Practice in England and Wales, the prevalence of cellulitis and abscess of finger and toe, and other cellulitis and abscess for patients consulting a physician, was 74 and 158 per 10,000 person years at risk, respectively. (McCormick et al, 1995) *Surgical Site Infections* Regardless of methodologies, hospital type, or time period, SSI are one of the most prevalent nosocomial infections. Globally, SSI are generally the third most commonly reported healthcare-associated infection. (Leaper et al, 2004; Mangram et al, 1999) Prevalence studies conducted in Europe report that 2-6% of all surgical patients developed a SSI. (Leaper et al, 2004) A 1996 point prevalence study in general academic and public French hospitals found that 11% of nosocomial infections were SSI, with rates ranging from 0.1% in eye surgery patients to 8% in vascular surgery patients (The French Prevalence Survey Study Group, 2000). SSI were one of the most prevalent infections in a 1-day point prevalence study in 2001 in 15 Italian hospitals; 15.6% of all nosocomial infections were SSI while among surgical patients, the prevalence of SSI was 5.2% (95% CI 3.3-7.1). (Nicastri et al, 2003) A higher prevalence of SSI was found in a point prevalence study in acute-care Norwegian hospitals. In 2002 and 2003 surveys, 28% of nosocomial infections were SSI. (Eriksen et al, 2005) Overall, 5-6% of patients undergoing a surgical procedure developed a SSI. (Eriksen et al, 2005) Data from surveillance studies across 26 community hospitals in southeastern U.S. report an annual prevalence of 1.13 deep and organ space infections per 100 surgical procedures in 2005. (Anderson et al, 2007) <u>*Staphylococcus aureus*</u> In a recent prospective study of invasive *S. aureus* infections in western Sweden, soft tissue infections (deep-seated abscesses) were the most prevalent diagnosis (27% of episodes). (Jacobsson et al, 2007) *Paediatric patients*

	Skin and soft tissue infections In a nationwide survey of paediatric patients in Finland with invasive group A streptococcus infections from 1996 to 2010, the most prevalent clinical diagnoses were severe soft tissue infection in 46% of children (Tapiainen et al, 2016). In a prospective study of all cases of invasive *S. aureus* infections (ISA) from 2003 to 2005 in Western Sweden, 8% of children with ISA had a soft tissue infection (Jacobsson et al, 2007). A retrospective analysis of primary diagnosis of SSTI in patients under 18 years of age from the 2000, 2003, and 2006 Kids' Inpatient Databases estimated the number of SSTIs in US children increased from 17,525 ± 838 admissions in 2000 (0.65% of paediatric hospitalisations) to 48,228 ± 2,223 (1.77% of paediatric hospitalisations) in 2006 (Lautz et al, 2011). In a New Zealand birth cohort, *S. aureus* was isolated from 43.4% of children at 4.5 years of age, and 29.4% of children were affected with SSTI before age 5 years (Hobbs et al, 2018). A retrospective analysis of discharge data for children with *S. aureus* infections from January 2002 through 2007 using the Paediatric Information System identified 57,794 children in the US with *S. aureus* infection (Gerber et al, 2009). The predominant infection cause by *S. aureus* infections were of skin and soft tissue infection, occurring in 40% of children (Gerber et al, 2009). See Section 1.7.1 (Potential Health Risk) for additional detail on the prevalence of etiologic agents in SSTI.

SI.1.3 Demographics of the population in the authorised or proposed indication - age, gender, ethnic origin, and risk factors for the disease

Table 5- Demographics of the population in the authorized or proposed indication

Demographic profile of target population	Overall, SSTI tend to occur in older patients. Elderly people are at increased risk for nosocomial and healthcare associated infections, such as skin and soft tissue infection. Some studies show a slight male predominance but generally there is no gender difference for development of SSTI. The demographic characteristics that follow are derived from the studies or sources previously described. Cellulitis The average age of hospitalised patients with cellulitis was 60 years with a slight female predominance (52%). (Carratala et al, 2003) Based on data from the 2004 U.S. NHDS, demographic characteristics of persons discharged with cellulitis and abscess as a first-listed diagnosis were as follows: (Kozak et al, 2006) Age: 9.6% (<15 years); 29.3% (15-44 years); 30.2% (45-64 years); 31% (65+ years) Gender: Male: 52.6%. Prevalence (per 10,000 population): by age: 8.8 (<15 years); 13.2 (15-44 years); 24.1 (45-64 years), 47.9 (>65 years); by gender: 20.6 (males) and 17.9 (females). Based on the 1991-1992 Morbidity Statistics from General Practice in England and Wales, demographic characteristics of persons consulting a physician for other cellulitis and abscess (ICD-9 code 682) were as follows: Prevalence (per 10,000 person years at risk): by age: 69 (0-4 years); 70 (5-15 years); 101 (16-24); 133 (15-44 years); 181 (45-64); 271 (65-74 years); 417 (75-84); 613 (>85 years) by gender: 140 (males); 176 (females). (McCormick et al, 1995) Based on the 1991-1992 Morbidity Statistics from General Practice in England and Wales, demographic characteristics of persons consulting a physician for cellulitis and abscess of finger and toe (ICD-9 code 681) were as follows: Prevalence (per 10,000 person years at risk): by age: 128 (0-4 years); 105 (5-15 years); 56 (16-24); 53 (15-44 years); 71 (45-64); 79 (65-74 years); 83 (75-84); 104 (>85 years) by gender: 73 (males); 75 (females). (McCormick et al, 1995) Surgical Site Infections Demographic data on persons with SSI were not detailed in published surveillance studies. *Staphylococcus aureus* The median age of persons with invasive *S. aureus* soft tissue infections in western Sweden was 74 years (range 4-93 years). (Jacobsson et al, 2007) *Paediatric population* Children with MRSA infection were more likely than those with MSSA infection to have skin and soft tissue infection (47% versus 33%; odds ratio: 1.75; 95% CI: 1.69-1.81) (Gerber et al, 2009).

Risk factors for the disease

Table 6- Risk factors for the disease

Potential health risk	Skin and soft tissue infections are considered complicated when they involve deeper soft tissues, such as fascia or muscle layers, require surgical intervention, or arise in the presence of significant co-morbidities, such as diabetes mellitus. ABSSSIs include secondary infections of diseased skin, acute wound infections (traumatic or bite-related), SSIs, and chronic wound infections and are among the most common infections treated in a hospital setting. (Lee et al, 2005) Certain diseases or conditions predispose patients to ABSSSI. Special patient populations at increased risk for a ABSSSI include the elderly, persons who have poor nutritional status, diabetes, current smokers, or are obese. (Itani, 2005; Turina and Cheadle, 2005; DiNubile and Lipsky, 2004) Similarly, patients who have other infections at a remote body site, patients who are colonised with other microorganisms, on steroids, or have undergone chemotherapy, and patients with a prolonged length of hospital stay or previous hospitalisation, are more prone to serious ABSSSI. (Itani, 2005) Despite the availability of many antibiotics, ABSSSIs encompass a complex of conditions and diseases that continue to be a significant cause of morbidity and mortality both in the nosocomial and community settings. In Scotland, soft tissue infections accounted for 10% of hospital admissions to an infectious disease unit. (Dykhuizen et al, 1994) Globally, *S. aureus* is the most frequent aetiologic pathogen implicated in ABSSSI. *Streptococcus pyogenes*, Group B beta-haemolytic streptococci (*Streptococcus agalactiae*), and group C and G streptococci are also common aetiological microbes in ABSSSI, but there are often mixed gram-positive and gram-negative aerobic and anaerobic bacteria as well. (DiNubile and Lipsky, 2004) Resistance is occurring across many gram-positive genera, including staphylococci, streptococci and enterococci; methicillin-resistant staphylococci, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci (VRE) are of particular interest (Jones et al, 2003; Jones et al, 2013, Diekema et al, 2004). Multi-drug resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), are an increasingly common cause of cSSTI, including SSI. (Wilson, 2003) Furthermore, infection by MRSA has been associated with a poor clinical outcome as compared to that with methicillin-susceptible isolates (Engemann et al, 2003; Melzer et al, 2003; Jones et al, 2003; Moellering, 2006; Abrahamian et al, 2008). The emergence of methicillin-resistant and vancomycin-resistant community-acquired and nosocomial Gram-positive pathogens has created a serious public health problem, worldwide increasing both mortality and healthcare costs. Infections with MRSA are an important cause of morbidity and an increased risk in mortality among hospital patients. The growing prevalence of MRSA infections not only poses a significant health risk but also represents a substantial economic burden. The Surveillance Network (TSN) in 2001 reported that *S. aureus* was the most prevalent bacterial pathogen of SSTI in hospitalised patients in France, Germany, Italy, Spain, and in the U.S. (Jones et al, 2003) The proportion of MRSA varied widely among countries, with the lowest prevalence in Germany (12%) compared with 32% and 35% in Spain and France, and 42% and 44% in Italy and the U.S. (Jones et al, 2003) Similar findings have been observed in the SENTRY surveillance programme which monitors hospital antimicrobial susceptibility patterns in SSTI in the U.S., Canada, Europe, Latin America, and the Western Pacific region. Over a 7-year period (1998-2004), *S. aureus* was the causative agent in more than one-third of SSTI, ranking highest in North America. (45%) and 38% in Europe. (Moet et al, 2007) The prevalence of MRSA among SSTI in Europe was 23%, with the rate varying greatly among the countries, ranging from 0.8% in Sweden to 50% in Portugal.(Moet et al, 2007) Prevalence data reported from 296 acute care hospitals in The Study of the Prevalence of Nosocomial Infections in Spain (EPINE) (1993-2003) estimates that 38% of all MRSA infections were nosocomial skin infections and 14% were community-acquired MRSA skin infections. The adjusted odds ratio of skin and soft tissue infections being caused by MRSA was 50% higher than for bloodstream infections (OR=1.5, 95% CI, 1.2-1.9). (Asensio et al, 2006) Data from surveillance studies across 26 community hospitals in south eastern U.S. show that *Staphylococcus aureus* was the most common (33%) isolate from deep and organ space SSI during 2005, yielding a prevalence rate of 3.7 per 1000 procedures. (Anderson et al, 2007) Overall, MRSA was isolated from 17% of SSI (overall annual prevalence rate of 2.0 infections per 1000 surgical

	procedures). (Anderson et al, 2007) The crude incidence of MRSA isolates from SSTI that required surgical debridement increased significantly from 2000 (34%) to 2006 (77%) (P<0.001) in a Texas (U.S.) Veterans Affairs Hospital; more than half (52%) of these patients had underlying diabetes mellitus. (Awad et al, 2007) The epidemiology of MRSA infection is changing, as MRSA has been historically considered a nosocomial pathogen while increasingly reports of community-associated isolates have been identified. In the past, cases of MRSA infection identified in the community had been linked to known risk factors such as recent hospitalisation, contact with a recently hospitalised individual, or previous antimicrobial therapy. More recently, community-acquired MRSA (CA-MRSA) infections have been described in children and adults without any obvious risk factors. (Chambers, 2001) Outbreaks of CA-MRSA skin infections have been reported (CDC, 2003; Moran et al, 2005; Nhan etal 2012) that are unrelated to the hospital acquired strains (Salgado et al, 2003; Klevens et al, 2007) and can include abscesses and cellulitis (Gorak et al, 1999). Nevertheless, necrotizing infections, bacteraemia, and fatal pneumonias have also been described (Lina et al, 1999; Klevens et al, 2007). Hospital-acquired MRSA (HA-MRSA) is more prevalent in long-term facility residents, patients who have diabetes, patients who have renal failure on dialysis, patients with a prolonged hospitalisation, and intensive care unit (ICU) patients. (Itani, 2005) Clusters and outbreaks of CA-MRSA have been reported among athletes participating in contact sports, military recruits, jail inmates, intravenous (IV) drug abusers, and institutionalised adults with developmental disabilities.(Borer et al, 2002; CDC, 2003; Lindenmayer et al, 1998; Zinderman et al, 2004) CA-MRSA is now the most common cause of CA soft tissue infections at major clinical care centers, such as the University of California, Los Angeles Medical Center (Moran et al, 2005) and among the military the majority of cellulitis caused by *S. aureus* is due to MRSA. (Landrum et al, 2012) CA-MRSA infections have been reported in North America and from various countries across Europe, including France, the Netherlands, Sweden, the United Kingdom, and in Australia and New Zealand. (Dufour et al, 2002; Lina et al, 1999; Osterlund et al, 2002; SCIEH, 2003; Vandenesch et al, 2003; Wannet, 2003) While the exact prevalence is unknown, reported rates of CA-MRSA vary widely among studies, in part due to the use of different definitions to distinguish CA-MRSA and HA-MRSA, but also because of the different settings in which studies have been performed. Relatively few studies are population-based; most studies are based on hospitalised patients or patients upon admission to the hospital, which may result in an overestimation of the true prevalence of CA-MRSA. A meta-analysis found the pooled prevalence of CA-MRSA was approximately one-third among hospitalised patients with MRSA; approximately 86% of all patients with CA-MRSA had >1 healthcare-associated risk factor (recent hospitalisation and chronic illness requiring health care visits were the most common). In studies which performed surveillance cultures in the community, the pooled prevalence of MRSA colonisation was 1.3% (95% confidence interval (CI); 1.04%-1.53%; range 0.4% to 7.4%); approximately 48% of colonised individuals had at least one risk factor. (Salgado et al, 2003) Skin and soft tissue infections were the predominant site of CA-MRSA, accounting for 75% of all CA-MRSA infections in the Minnesota area (U.S.).(Naimi et al, 2003) In a prospective study of MRSA infections at U.S. military medical clinics and hospitals in San Diego (1990-2004), 65% were cases of CA-MRSA, with SSTI as the major site of infection in 95% of CA-MRSA infections. (Crum et al, 2006) *Paediatric patients* According to analysis of the 2000, 2003, and 2006 Kids' Inpatient Databases, paediatric SSTI admissions in the US have increased in both number and proportionate to all hospital admissions, disproportionately affecting children younger than 3 years (Lautz et al, 2011). In a cross-sectional study of emergency department visits in the US between 2006 and 2016, paediatric patients with cellulitis or erysipelas were associated with higher odds of methicillin-resistant *S. aureus,* and those with antibiotic-resistant infections were associated with increased odds for chronic inflammatory skin disease. (Ren and Silverberg 2021).

SI.1.4 The main existing treatment options

Table 7- Main treatment options

Main treatment options	A variety of approved alternatives for the treatment of ABSSSI caused by gram-positive pathogens were available during the clinical development program. A comparison of the most important features from product labeling and other sources reveals the following for these treatment alternatives: Vancomycin has a well-established safety profile with decades of use in the US and EU. Its use is associated with 'rare' anaphylactic and hypersensitivity reactions, 'rare' nephrotoxicity, 'uncommon' transient or permanent loss of hearing, and the requirement for monitoring of neurotoxicity and ototoxicity (Vancomycin Actavis SmPC, 2013). The anti-staphylococcal cephalosporins require multiple daily regimens and are not active against MRSA. Ceftaroline fosamil (Zinforo SmPC, 2012) approved in the US and Europe, does have activity against MRSA. It is dosed intravenously twice daily and has been associated with serious, occasionally fatal hypersensitivity reactions. *Clostridium difficile*-associated diarrhoea and antibacterial-associated colitis and pseudomembranous colitis have been reported with ceftaroline fosamil and may range in severity from mild to life threatening. Quinupristin/ dalfopristin (Synercid PI, 2007) requires administration via central venous catheter, and is associated with frequent myalgias/ arthralgias, poor injection site tolerability, occasional hyperbilirubinemia, cytochrome P450 drug-drug interaction potential, and multiple daily dosing regimens. Linezolid (Zyvox SmPC, 2013), is a reversible, nonselective inhibitor of monoamine oxidase reactions, and has been associated with myelosuppression (thrombocytopenia, dose and duration-dependent); rare lactic acidosis; and rare neuropathy with prolonged therapy. Linezolid requires BID dosing. Daptomycin (Cubicin SmPC, 2012) is a approved for cSSTI with activity against MRSA. Caution should be used in patients with renal or hepatic impairment. Regular monitoring of renal function is advised during concomitant administration of potentially nephrotoxic agents, regardless of the patient's pre-existing renal function. *Clostridium difficile*-associated diarrhoea has also been observed at an unknown frequency. Teicoplanin (Targocid SmPC, 2014) has been approved in the EU for the treatment of moderate to severe infections due to gram-positive bacteria, including SSTIs. Teicoplanin is less toxic than vancomycin, and is generally well tolerated. However, unlike dalbavancin, it requires daily (or twice daily) administration and dose reduction in haemodialysed patients. Additionally, it must be used with care in conjunction with or sequentially with, other drugs with known nephrotoxic or ototoxic potential. Thrombocytopenia has been reported with teicoplanin. Tigecycline (Tygacil SmPC, 2013), has also become available for the treatment of cSSTIs. Like teicoplanin, tigecycline requires twice daily dosing. It is less well tolerated, being very commonly associated with nausea (35%) and vomiting (20%). An increase in all-cause mortality has been observed across phase 3 and phase 4 clinical trials in TYGACIL-treated patients versus comparator. Hepatic dysfunction and liver failure as well as pancreatitis have been reported and lower cure rates and higher mortality were seen when patients with ventilator-associated pneumonia were treated with tigecycline. Orbactiv (Oritavancin package insert, 2019) has been approved in the EU for the treatment of ABSSSI and is administered as a single infusion over 3 hours. It is associated with nausea, hypersensitivity reactions, infusion site reactions, and headaches. The most common adverse effects leading to treatment discontinuation in pooled ABSSSI clinical trials are cellulitis and osteomyelitis.

SI.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Table 8- Mortality and morbidity

Mortality in target Indication	ABSSSI are a significant source of morbidity and mortality in the nosocomial and community settings, despite improved understanding of risk factors and an array of antibiotics and prophylactic measures that can be instituted. (Wilson, 2003; Spellberg et al, 2009) Limited data exist on mortality associated with ABSSSI as a disease state; however, data are available on sub-categories of ABSSSI and mortality associated MRSA infection. Cellulitis In a university hospital in Barcelona, Spain, a retrospective chart review of persons hospitalised for community-acquired cellulitis found overall mortality (<30 days) of infectious cellulitis was 5% (16/332 cases); cause of death was mainly shock or underlying disease. (Carratala et al, 2003) Surgical Site Infections In the U.S., a case-control study found that surgical patients (all specialties) with SSI were twice as likely to die during postoperative hospitalisation as those persons without SSI (RR, 2.2 (95% CI, 1.1-4.5)). SSI from gastrointestinal surgery was associated with the highest mortality. (Kirkland et al, 1999) Over a three-year period in Northern France, a SSI surveillance group reported a crude mortality rate of 5.8% among surgical patients with a SSI (adjusted OR, 1.6 (95% CI, 1.3-2.2). Of these, 38% of deaths were directly attributable to the infection. (Astagneau et al, 2001) A prospective study in three Spanish hospitals found that organ/space SSIs were associated with a higher severity of disease; these patients were at an increased risk of in-hospital mortality (adjusted OR, 4.9 (95% CI, 1.5-15.6)). (Delgado-Rodriguez et al, 1999) MRSA Among patients with a SSI (primarily associated with cardiothoracic or orthopaedic procedures) in two community hospitals in the U.S., the presence of MRSA in a surgical incision was associated with a 3-fold increased risk in 90-day postoperative mortality compared with patients with methicillin-sensitive *S. aureus* (MSSA) infections (adjusted OR, 3.4 (95% CI, 1.5- 7.2)). This nested-case control study found that persons with MRSA-infected SSI had >12-fold higher risk of 90-day postoperative mortality than controls without SSI (OR, 12.3 (95% CI, 4.2-36.4). (Engemann et al, 2003)

SI.1.6. Important co-morbidities

Patients with ABSSSIs typically have co-morbidities for which the infections become complicated and more difficult to treat. These are primarily diabetes mellitus, vascular disease, and decreased liver and renal function. Patients with decreased liver function enrolled in dalbavancin clinical trials were mainly alcoholic or IV drug abusers. Available published epidemiological estimates for these co-morbidities in the context of ABSSSI are extremely limited.

Currently available data from different population-based samples, including the general population and patients with SSTI overall, are summarised below.

Table 9- Diabetes Mellitus

Incidence	The international diabetes federation states that globally 366 million people (8.3%) have diabetes (2011), however they estimate that by 2030 this will have risen to approximately 552 million (9.9%). In addition 183 million peoplehave undiagnosed diabetes. (Wild et al, 2004) It is well known that persons with diabetes mellitus are at an increased risk of infection, especially SSTI including lower extremity infections. (Calvet and Yoshikawa, 2001; Shah and Hux, 2003) Along with an increased susceptibility to infection, persons with diabetes may have associated co-morbidities, including peripheral vascular disease, that may affect the course of soft tissue infection. Lower extremity infection is a major source of morbidity and a leading cause of hospitalisation for persons with diabetes. Cellulitis A prospective cohort study of type 1 and type 2 diabetes mellitus was conducted using the Second Dutch National Survey of General Practice (2000-2002), in which persons with type 1 and 2 diabetes had a greater incidence of cellulitis (0.7%) compared with control patients with hypertension (0.3%). (Muller et al, 2005) In a university hospital in Barcelona, Spain, a retrospective chart review of persons hospitalised for community-acquired cellulitis found that 25% of persons with infectious cellulitis (excluding cellulitis complicating diabetic foot ulcers) had diabetes mellitus. (Carratala et al, 2003) Surgical Site Infections Persons with diabetes may be predisposed to surgical wound infections with a possible causal relationship to poor glycaemic control. (Golden et al, 1999; Boyko and Lipsky, 1995) An analysis of 1999 hospital discharge data from the universal health care system in Ontario, Canada, found that patients with diabetes were at an increased risk for postoperative infections (RR, 2.02 (99% CI, 1.80-2.27)) compared with patients without diabetes. (Shah and Hux, 2003) *Paediatric patients* There were no published data found on the incidence of diabetics in paediatric patients with soft skin infection. However, the incidence of diabetes type 1 and 2 in the general population of paediatric patients aged 0-19 years in Kronoberg, Sweden was 37.8 (95% CI, 36.1–39.6) and 3.1 (2.6–3.6), respectively (Thunander 2008). The British Paediatric Surveillance Unit (BPSU) prospectively followed paediatricians from April 2015 to April 2016 and reported the incidence of type 2 diabetes in children of all ethnicities aged 0–16 years was 0.78 per 100,000 per year in England and Wales (Candler 2018).
Prevalence	The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The National Health and Nutrition Examination Survey (NHANES) reported that the crude prevalence of diagnosed diabetes in adults age 20 and older was 7.7% in 2005-2006. Including those with undiagnosed diabetes who met diagnostic criteria, crude prevalence increased to 12.9%. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people over 65 years of age and the increase in obesity. (Wild et al, 2004; Cowie et al, 2009). Surgical Site Infections Based on the cohort study by Engemann and colleagues of 479 surgical patients who developed SSI, the prevalence of diabetes was 34.5% among persons with MSSA SSI and 48.8% among those with MRSA SSI. (Engemann et al, 2003) *Paediatric patients* Cellulitis A cross-sectional study of the 2006 to 2016 National Emergency Department Sample of US Emergency Department visits reported a weighted prevalence of 0.32% (0.30-0.33) for diabetes mellitus in children with a diagnosis of cellulitis or erysipelas in the Emergency Department (Ren and Silverberg 2021).
Mortality	One in 10 deaths in adults in the Europe Region can be attributed to diabetes, representing close to 600,000 people in 2011 (International Diabetes Federation). The vast majority (90%) of these deaths were in those over the age of 50. There are slightly more deaths due to diabetes in women compared to men (316,000 vs 281,000 respectively).

Concomitant medications	People with diabetes tend to use many medications, both to treat hyperglycaemia and for the prevention and treatment of sequelae like cardiovascular and renal disease. Most commonly, persons with diabetes take oral hypoglycaemics (e.g. metformin), insulin, HMG CoA-reductase inhibitors (statins), antiplatelet agents (e.g. aspirin), and antihypertensives, especially angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Those with overt vascular disease not only use a medication from each of these classes, but appropriately take multiple drugs from each class for aggressive prevention of cardiovascular-related mortality. (ADA, 2007; Smith et al, 2006)

Table 10- Peripheral Vascular Disease

Incidence	One publication was found referencing co-morbid vascular disease, in particular peripheral arterial disease (PAD), in patients with cSSTI. A hospital-based observational study in ten European centres estimated the prevalence of PAD (defined as ankle brachial index (ABI) <0.9 and/or two absent foot pulses) to be 31% among diabetic patients presenting with a new infected foot ulcer (defined as a full-thickness lesion below the ankle). (Prompers et al, 2007) To supplement these data, available epidemiologic data of PAD in different population-based samples are described. The crude incidence of PAD (ABI <0.90 at two consecutive visits or any PAD-related lower-extremity amputation) was 3.7 per 100 patient years among patients with type 2 diabetes enrolled in the prospective observational community-based study in Western Australia (The Fremantle Diabetes Study). (Norman et al, 2006)
Prevalence	Data on prevalence of peripheral vascular disease in ABSSSI patients were not found. Population-based studies estimate the prevalence of PAD to be 4% to 19% dependent on the definition of PAD and the age of study participants. Using U.S. NHANES data from 1999-2004, the prevalence of PAD (ABI <0.9 in either leg) in adults aged 40 years or older was lowest in persons with normal fasting glucose levels (<100 mg/dL) (3.9%, 95% CI, 2.7–5.0%) and impaired fasting glucose (fasting plasma glucose 100-125 mg/dL) (5.4%, 95% CI, 4.0-6.8%) and highest among persons with undiagnosed (9.2%, 95% CI, 4.4-14.0%) and diagnosed (7.5%, 95% CI, 4.1-11.0%) diabetes mellitus. (Gregg et al, 2007) Utilising the same survey data, Ostchega and colleagues estimated the crude prevalence of PAD in persons aged 60 years or older to be 11.6% (95% CI, 10.3-12.9%). Of these persons, approximately 30% were symptomatic (i.e., reported calf pain when walking). No statistical difference in age-adjusted PAD prevalence was noted between men (12.5%) and women (12.0%) whereas age-adjusted prevalence of PAD was higher in non-Hispanic blacks (19.5%, P=0.001) and Mexican Americans (15.6%, P=0.02) than in non-Hispanic whites (11.7%). (Ostchega et al, 2007) In a population-based study of 6450 men and women aged 55 years and older living in Rotterdam, the Netherlands, the prevalence of PAD was 19% (95% CI, 18-20%) when defined as ABI <0.9 and 8% (95% CI, 7-9%) when PAD was defined as ABI <0.70.[142] While persons aged 80 years or older had the highest PAD prevalence, after adjusting for age, no major gender differences were noted. (Meijer et al, 2000). In a population-based sample of Swedish residents aged 60 to 90 years, an estimated 18% (95% CI, 16.0-19.9%) of persons had PAD (ABI <0.9, asymptomatic or symptomatic) and 11.1% (95% CI 9.5-12.8%) had asymptomatic PAD. Women had a higher prevalence of PAD than men: 12.6% of women and 9.4% of the men had asymptomatic (i.e., PAD diagnosed with ABI only) PAD. (Sigvant et al, 2007)
Mortality	Lower extremity peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and is associated with increased cardiovascular morbidity and mortality. Patients with PAD have a 3-fold increased risk of dying from all causes and a 6-fold increased risk to die from cardiovascular disease within a period of 10 years compared with patients without PAD (Feringa et al, 2007) Patients with ABI <0.90 were more likely to die from cardiac illnesses than persons with ABI of 0.91-1.40 (HR=1.67, 95% CI, 1.13-2.47, P=0.010). (Norman et al, 2006)
Concomitant medications	Persons with PAD use medications to minimise cardiovascular and cerebrovascular events, prevent disease progression, and improve their quality of life by reducing or eliminating symptoms. Risk factor modifications that control blood pressure, lipids, and glucose levels, as well as smoking cessation, may require the use of pharmacological therapies. Antithrombotic therapy, such as aspirin or clopidogrel, are widely used for preventing cardiovascular events in these patients. (Watson et al, 2006)

Table 11- Decreased Renal Function

<table>
<tr><td>Incidence</td><td>Extensive search of the literature did not provide data on the global incidence of impaired renal function, nor were data found on impaired renal function in the target population. This could in part be due to the differences in categorisation of impaired renal function, or overshadowing by the more serious form ‘renal failure’ and/or associated co-morbidities i.e, diabetes mellitus, and high blood pressure. Data on impaired renal function in a clinical trial setting is available, however, the exclusion criteria for most studies makes this inappropriate to use.

The Centres for Disease Control and Prevention in the United States estimate that 10% (20 million) people aged over 20 years have some form of chronic kidney disease. Of these approximately 35% are associated with diabetes mellitus and 20% are associated with hypertension. (CDC, 2010).

Paediatric patients
No published data was found on the incidence of decreased renal function in pediatric patients with soft skin infection. However, the incidence of chronic kidney disease (stages 3-5) in children in the general population aged <1 year was an estimated 1 in 10,000 live births at a German hospital (Wedekin 2008). Analysis of paediatric data from registries in 37 European countries of patients with end stage renal disease starting renal replacement therapy between 2009 and 2011 reported an incidence of 5.5 cases per million of age-related population (pmarp) in patients aged 0-14 years (Chesnaye 2014).</td></tr>
<tr><td>Prevalence</td><td>NHANES III data show the prevalence of impaired renal function increases with age:
<table>
<tr><th>GFR mL/min/1.73m^2</th><th>20-39 years</th><th>40-59 years</th><th>60-69 years</th><th>≥70 years</th></tr>
<tr><td>≥90</td><td>86.0%</td><td>55.7%</td><td>38.5%</td><td>25.5%</td></tr>
<tr><td>60-89</td><td>13.7%</td><td>42.7%</td><td>53.8%</td><td>48.5%</td></tr>
<tr><td>30-59</td><td>-</td><td>1.8%</td><td>7.1%</td><td>24.6%</td></tr>
<tr><td>15-29</td><td>-</td><td>-</td><td>-</td><td>1.3%</td></tr>
<tr><td>N (Millions)</td><td>82</td><td>55</td><td>20</td><td>20</td></tr>
</table>

The prevalence of kidney failure is greater in the over 65 years. While chronic kidney disease is more common among women, men are 50% more likely to develop kidney failure than women. As well as gender difference, ethnicity also plays a part in the prevalence of impaired renal function with African Americans nearly four times more likely to develop kidney failure than Caucasians and Hispanics are 1.5 times more likely to develop kidney failure compared to non-Hispanic whites. (CDC, 2010) Data on prevalence of impaired renal function in ABSSSI patients were not found.

Paediatric patients
No published data was found on the prevalence of decreased renal function in pediatric patients with soft skin infection. However, the prevalence of paediatric patients in the general population was reported. Among children aged 0 to 14 years receiving renal replacement therapy in European countries increased with age; prevalence was 13.5cases pmarp in children aged 0–4 years, 26.4 pmarp in children aged 5-9 years and 44.4 pmarp in children aged 10–14 years (Chesnaye 2014).</td></tr>
<tr><td>Mortality</td><td>Impaired renal function is an important risk factor for other diseases including: cardiovascular disease, kidney failure or end stage disease and premature death. Risk factors for the progression of impaired renal function include: hypertension, inadequately controlled diabetes, obesity, elevated cholesterol, family history or kidney injury due to physical trauma or toxins. In some cases renal impairment is reversible if the causative agent is removed. However, if there is chronic prolonged exposure the kidney may become permanently damaged and eventually fail.</td></tr>
<tr><td>Concomitant medications</td><td>Patients with impaired renal function may not require medication per se; it is dependent wholly on the level of impairment. Co-morbidities or risk factors associated with the condition may involve the use of medications to treat hyperglycaemia, hypertension, and cardiovascular disease.</td></tr>
</table>

Table 12- Decreased Liver Function

Incidence	A search of the literature did not provide data on the global incidence of impaired hepatic function in the target population. Data on impaired hepatic function due to different causes or in a clinical trial setting were available but were not relevant for this RMP.
Prevalence	Alcohol abuse is one of the most common causes of liver disorders including cirrhosis. The true prevalence of alcoholic hepatitis (AH) is unknown, but a histologic study conducted in France suggests that AH may be present in as many as 50% of hospitalized alcoholic patients. (Trabut, 2008) Data on prevalence of impaired hepatic function in ABSSSI patients were not found.
Mortality	The consequence of impaired hepatic function is dependent on the level of impairment and the cause. In some cases hepatic impairment is reversible if the causative agent is removed. However, if there is chronic prolonged exposure the liver may become permanently damaged and eventually fail. In 2003, 44% of all deaths from liver disease in the US were attributed to alcohol (Yoon, 2006).
Concomitant medications	Patients with impaired hepatic function may not require medication per se; it is dependent wholly on the level of impairment. Co-morbidities or risk factors associated with the condition may require the use of medications to treat viral infections, cancer, gallbladder disease, IV drug abuse and alcoholism.

Table 13- Alcoholism

Incidence	Data on the incidence of alcoholism in the target population were not found. The Global Burden of Disease study estimated the incidence of alcohol abuse disorder in 2016 at 50,432,000 people worldwide. (GBD 2017) Data on prevalence of alcohol abuse disorder in ABSSSI patients were not found.
Prevalence	Data on prevalence of alcohol abuse disorder in ABSSSI patients were not found. According to WHO, global prevalence rates of alcohol use disorders among adults were estimated to range from 0% to 16% in 2004, with the highest prevalence rates to be found in Eastern Europe (WHO, 2011). The Global Burden of Disease study estimates the prevalence of alcohol abuse disorder in 2016 at 100,389,000. (GBD 2017) The experience in the dalbavancin clinical trial program has demonstrated that alcoholic misuse is frequently present in the target population, although exact numbers are not known. Alcoholism was one of the main causes for elevated serum aminotransferases observed in clinical trials with dalbavancin. Treatment with a weekly dose of dalbavancin may be more convenient and ensure better compliance in this subgroup of patients compared to daily dosing of some of the alternative antibacterials.
Mortality	In 2004, 3.8% of all global deaths were attributable to alcohol, 6.2% for men and 1.1% for women. Intentional and unintentional injuries were the most common alcohol-attributable causes of death, responsible for around 40% of such fatalities. 16.6 % of all alcohol-attributable deaths were due to cirrhosis, and almost 50% of all deaths due to cirrhosis were attributed to alcohol worldwide (WHO, 2011).
Concomitant medications	There are no specific medications typically used in the population with alcoholism or binge drinking. However, this population may be more prone to illicit drug use.

Table 14- IV Drug Abuse

Incidence	Data on the incidence of IV drug abuse in the target population were not found.
Prevalence	Cutaneous injection-related infections (CIRI), such as abscesses and cellulitis, are common among injection drug users. A study on a prospective cohort of injection drug users found the prevalence of abscesses to be 21.5% within a six month period (Lloyd-Smith, 2005) With regard to injecting drug use, the United Nations Office on Drugs and Crime (UNODC), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the World Bank and the World Health Organization (WHO), drawing on the most recent data available, jointly estimate that the number of people who inject drugs is 12.7 million (range: 8.9 million-22.4 million). That corresponds to a prevalence of 0.27 per cent (range: 0.19-0.48 per cent) of the population aged 15-64. (UNODC, 2014) In the DISCOVER programme, patients with IV drug abuse were included and approximately 15 % of the patients had a history of IV drug abuse. In the DUR001-303 clinical trial assessing the single dose dalbavancin regimen (1500 mg) to the two-dose regimen (1000 mg on Day 1 and 500 mg on Day 8), approximately 30% of the patients had a history of iv drug abuse (Gonzalez, 2018). Dalbavancin may be considered for use in this sub-group of patients given the enhanced convenience and better compliance with the once-weekly dosing regimen.
Mortality	According to WHO, most of the deaths among drug users are due to HIV, overdose, suicide and trauma. In 2004, 45,000 deaths due to illicit drugs were recorded in the European Region. Global estimates suggest that 245,000 deaths are attributable to illicit drugs each year (WHO 2004).
Concomitant medications	Patients using illicit IV drugs may also use other illicit drugs and alcohol.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

A comprehensive safety evaluation of dalbavancin was performed including, single and repeat dose toxicity, genotoxicity, reproductive and developmental toxicity, local tolerance as well as immunotoxicity. Additional nonclinical studies included safety pharmacology studies and secondary pharmacodynamics, including an assessment of the potential effects on a large number of enzyme, receptors, ion channels and uptake sites.

Animal toxicology studies to support the clinical investigation and registration of dalbavancin were conducted in mice, rats, dogs, rabbits, and minipigs. The duration of exposure of these animals would support dosing in humans up to 3 months. Because pharmacokinetic (PK) differences exist between animals and humans, daily dosing was performed to conservatively evaluate toxicity during repeated exposure. The total exposure (area under the curve [AUC]) from the 2-dose regimen in subjects, as determined from population PK analyses, was compared to the steady-state exposure in animals over the entire dosing period (28 or 90 days). The total AUC in subjects on the standard clinical dosing regimen was estimated from population PK analysis to be approximately 26000 μg•h/mL. During the dosing interval (28 or 90 days) at the no-observed adverse effect level (NOAEL) or tolerated doses, the exposure levels (based on AUC) in animals are at least double (2- to 13-fold) to those in humans during the clinical dosing regimen.

The following potential safety concerns were identified in the safety pharmacology and toxicology program:

- Renal toxicity in rats and dogs
- Liver toxicity in rats and dogs
- Reproductive and developmental toxicity in rats and rabbits
- Transient infusion reactions in dogs

No toxicological effects were seen on the central and autonomic nervous systems, cardiovascular system, or respiratory system. Also, no pancreatic beta-cell morphologic effects of any kind were observed at any dose level in the toxicology studies of dalbavancin in rats and dogs and no treatment-related pancreatic changes of any kind were observed in dalbavancin-treated dogs.

SII.1 Key safety findings from non-clinical studies and relevance to human usage (for each safety finding)

Table 15- Summary of Non-Clinical Safety Findings

Key Safety findings (from non - clinical studies)	Relevance to human usage
Renal Toxicity	
Dose-dependent and evident at ≥20 mg/kg/day in 28-day studies and ≥10 mg/kg/day in 90-day studies in rats and dogs. Generally more severe in dogs compared to rats at the same dose and duration. In 4-week studies, was characterized at 20 mg/kg/day in rats and/or dogs by reduced urine specific gravity, increased urine pH, increased urine erythrocytes, increased relative renal weight, macroscopic renal pallor, and microscopic tubular changes (dilatation, degeneration, necrosis, and basophilia) and interstitial inflammation; and additionally at ≥40 mg/kg/day in rats and/or dogs by increased serum urea and/or creatinine, increased urine volume, increased absolute renal weight, macroscopic renal mottling or roughened surfaces, and microscopic tubular casts, and fibrosis. In 90-day studies, was characterized at 10 mg/kg/day in rats by mild increases in serum urea, urine red blood cells (RBC) content, and renal weight; and in dogs at ≥10 mg/kg/day by microscopic renal tubular necrosis and inflammation and additionally at 40 mg/kg/day by marked increases in serum urea and creatinine, increased renal size and weight, macroscopic renal pallor, and glomerular mesangial proliferation. At 40 mg/kg/day, 2 male dogs were euthanized and their moribund condition was partly attributed to renal failure. Reversible, but residual renal fibrosis (also referred to as sclerosis) was observed after administration of doses ≥40 mg/kg/day for ≥4 weeks. NOAELs for kidney were 10 mg/kg/day for 28 days of dosing and 5 mg/kg/day for 90 days of dosing	Renal findings were observed in non-clinical studies at systemic exposures >2-fold higher than the human AUC. No evidence of renal adverse events above the comparator agents were identified in the dalbavancin clinical development program. As such dalbavancin at the recommended dose appears to pose a minimal risk to humans
Liver toxicity	
Was 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. The NOAELs for liver were 20 mg/kg/day for 4 weeks of dosing and 5 mg/kg/day for 90 days of dosing. Was more consistently characterized by clinical chemistry changes (especially increased aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) than by histologic effects. Transaminase elevations were observed earlier than histologic or other changes, persisted after histologic findings had reversed, and were the predominant findings in rats. Dose-dependent hepatocellular necrosis was observed in dogs dosed at ≥10 mg/kg/day for longer than 2 months. The toxicity was reversible, but residual hepatic fibrosis was observed after administration of 40 mg/kg/day for 90 days in dogs. The NOAELs for liver were 20 mg/kg/day for 4 weeks of dosing and 5 mg/kg/day for 90 days of dosing	Hepatic findings were observed in non-clinical studies at systemic exposures >6-fold higher than the human AUC. No evidence of hepatic adverse events above the comparator agents were identified in the dalbavancin clinical development program. As such dalbavancin at the recommended dose appears to pose a minimal risk to humans

Key Safety findings (from non - clinical studies)	Relevance to human usage
Reproductive and developmental toxicity in rats and rabbits.	
Reproductive toxicity studies in rats and rabbits showed no evidence of a teratogenic effect. Dalbavancin crosses the placenta and is excreted into milk in rats. In rats, the paternal and maternal NOELs, as well as NOELs for mating and fertility and embryo-foetal development, were 15 mg/kg/day (1.2 times the human dose on an exposure basis). The NOEL for viability and growth in offspring was 30 mg/kg/day. At 45 mg/kg/day in rats (3.5 times the human dose on exposure basis) there was reduced fertility and an increased incidence of embryo-lethality, reductions in fetal weight and skeletal ossification and increased neonatal mortality. Reduction in fertility in rats was attributed to renal impairment at the 45 mg/kg/day dose, as male rats with renal impairment and uraemia are known to be hypoandrogenic and infertile. In rabbits, abortion occurred in conjunction with maternal toxicity at 15 mg/kg/day, the highest dose tested (0.7 times the human dose on an exposure basis) and was the developmental NOEL. The maternal NOEL was 5 mg/kg/day.	Based upon results from animal reproduction studies dalbavancin should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit outweighs the possible risk to the foetus. An effect on male fertility is not anticipated in humans since these effects in animals were only observed in association with renal toxicity and uraemia. The clinical relevance of the maternal effects seen in rabbits on pregnant or lactating females is unknown. Therefore, dalbavancin should not be used during pregnancy unless clearly necessary.
Transient infusion reactions in dogs	
Dogs given intravenous dalbavancin at doses ≥30 mg/kg/day, either acutely or in repeat dose studies, experienced transient infusion-related reactions in a dose-related manner. These reactions were characterized by modest hemodynamic changes (decreases in blood pressure and increases in heart rate), ear skin and scleral vessel congestion, muzzle, and/or paw swelling, mucosal pallor, salivation, vomiting, and sedation. These infusion reactions in dogs were attributed to histamine release and may reflect a combination of the size of the administered dose and/or dose solution concentration and the rate of infusion (Wold and Turnipseed, 1981; Masini et al, 1985). Infusion reactions attributed to histamine release (erythema and pruritus, also known as Red-man syndrome) have been recognized with infusion of glycopeptide antibacterials, including dalbavancin, in humans and appear to correlate with rate of infusion. No other acute systemic clinical signs were observed in association with dalbavancin infusion, consistent with an absence of findings in safety pharmacology studies (except for the hemodynamic effects in dogs) and the bacteria-specific nature of dalbavancin's mechanism of action. Similar changes were not observed in rats.	The transient infusion reactions seen in the studies with dogs were attributed to histamine release. The effect seen in dogs may reflect a combination of the size of the administered dose and/or dose solution concentration and the rate of infusion (generally less than 10 minutes). In humans, rapid intravenous infusions of glycopeptide antibacterial agents can cause reactions that resemble "Red-Man Syndrome," including flushing of the upper body, urticaria, pruritus, and/or rash. Stopping or slowing the infusion may result in cessation of these reactions. Therefore, dalbavancin is to be administered via intravenous infusion, using a total infusion time of 30 minutes to minimise the risk of infusion-related reactions.
Immunotoxicity	
Immunotoxicity NOELs in male and female rats were 10 and 40 mg/kg/day, respectively during 28 days. The NOEL was 10 mg/kg/day for male rats because of a statistically significant decrease in the humoral immune response, and was 40 mg/kg/day in female rats. The biologic significance of this was unclear as there was no consistent pattern of changes in cell population that correlated with the assay response, no evidence of a comparable effect in females, and no evidence of an increase in infections in rats or other consequences that were considered indicative of impaired humoral immune response.	The effects seen in the immune system (lymphoid depletion or necrosis in spleen, lymph nodes, and thymus of dogs treated at 40 mg/kg/day for at least 28 days) were considered secondary to other manifestations of systemic toxicity and are not considered to indicate a specific immunotoxic effect of dalbavancin.

The toxicological effects of dalbavancin at clinically relevant doses appear to reflect its local irritancy and slow systemic elimination. The plasma exposures in animals at the NOAELs in repeat dose toxicity studies 28 to 90 days long (ie, 2- to 6.5-fold the proposed clinical exposure period for ABSSSI) are at least twice that of the clinical plasma exposures. The only adverse finding observed at exposures in animals that were comparable to clinical exposure was in the area of reproductive toxicity (the occurrence of abortions in rabbits, but not rats).

The recommendation for avoiding use of dalbavancin in pregnant or lactating women is described in the Summary of Product Characteristic (SmPC) thus, additional non-clinical studies are not required in relation to these special populations. The genotoxicity and carcinogenicity studies showed no discernible genotoxic and carcinogenic potential for dalbavancin. A Paediatric Investigational Plan (PIP) has been agreed to and the additional preclinical studies in juvenile animals did not show an additional risk in the paediatric populations.

There is no need for additional non-clinical data in relation to use in special populations.

Recommendations for use of dalbavancin in renal- or hepatic impaired populations and instructions how to minimize the risk of infusion-related reactions are addressed in the SmPC.

SII.2 Conclusions on non-clinical data

Table 16- Conclusions of Non-Clinical Safety Concerns

Safety concerns	
Important identified risks (confirmed by clinical data)	Hypersensitivity
Important potential risks (not refuted by clinical data or which are of unknown significance)	Hepatic disorders Nephrotoxicity
Missing information	Reproductive and developmental toxicity

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Brief overview of development

The clinical development of dalbavancin was performed in concordance with standard approaches as used for the evaluation of newer antibacterial agents according to Good Clinical Practice. Dalbavancin was originally discovered by Biosearch Italia, which underwent a number of corporate acquisitions until it was finally acquired by Pfizer Ltd from Vicuron. As a consequence the clinical programme in adults had been conducted by several companies and Pfizer performed the first PIP pharmacokinetic study. On 21 Dec 2009, Durata Therapeutics acquired the dalbavancin programme from Pfizer and thereafter reinitiated clinical development of the compound, including 2 additional pivotal phase 3 studies DUR001-301 and DUR001-302 (comparing the dalbavancin 2-dose regimen to vancomycin IV/linezolid po for 10-14 days), and a subsequent pivotal phase 3 study DUR001-303 (comparing the dalbavancin single dose regimen to the 2-dose regimen). All studies were subject to regular monitoring by the Sponsor or an appointed Contract Research Organization.

Following phase 1 studies to determine the initial safety and tolerability profile, a focused phase 2 programme was conducted to elucidate the compound's potential utility in SSTI via assessment of two different dose regimens in patients with SSTI. An additional trial was performed to evaluate dalbavancin for the treatment of catheter-related bloodstream infections (CRBSI). This indication is not being pursued at the present time. Prior to Durata clinical program, the initial phase 3 programme evaluated dalbavancin therapy of both cSSTI and uncomplicated SSTI in patients who warranted parenteral therapy, with particular attention to those SSTI caused by MRSA. This was subsequently followed by 2 additional phase 3 clinical studies that evaluated dalbavancin therapy for the treatment of ABSSSI.

SIII.2 Clinical Trial exposure

The Phase 2/3 portion of the dalbavancin clinical development programme was largely based upon the 2-dose regimen of dalbavancin administered once weekly. This was the basis for the currently approved recommended dosing of dalbavancin in adult patients with ABSSSI as 1000 mg on Day 1 followed by 500 mg on Day 8. An additional study, DUR001-303, compared the efficacy and safety of single dose dalbavancin to a two dose regimen of dalbavancin for the treatment of acute bacterial skin and skin structure infections. A type II variation was approved by the EMA to amend the posology to include an alternative dosing regimen of 1500 mg administered as a single infusion.

Cumulatively through 22 May 2021, an estimated 4511 subjects have been enrolled in the dalbavancin clinical development program (including ongoing and completed clinical trials), of which 3123 adult and paediatric subjects have received dalbavancin. A cumulative summary of all patients exposed to dalbavancin since the developmental international birth date (26 January 1999; DIBD) is provided in Table 17. Study VER001-3 was not included due to dosing schedules that were dramatically different from the proposed dosing schedule. A cumulative summary of all adult patients exposed to dalbavancin in the Phase 2/3 clinical developmental program by study is provided in Table 18.

Table 17- Cumulative subject exposure from clinical trials by Treatment Group[1]

Treatment	Number of Subjects
Dalbavancin	3123
Active Comparator	1316
Placebo	72

[1] The 3 patients dosed in the VER001-3 study are not included.

Table 18- Extent of Exposure: Phase 2/3 Adult Overall Safety Population

Study number (Phase)	No. of patients exposed to dalbavancin	Age Range
VER001-4 (Phase 2)	40	16-85
VER001-5 (Phase 2)	41	18-86
VER001-9 (Phase 3)	571	18-93
VER001-16 (Phase 3)	107	18-86
VER001-8 (Phase 3)	367	18-89
DUR001-301 (Phase 3)	284	18-84
DUR001-302 (Phase 3)	368	18-85
DUR001-303 (Phase 3)	695	18-85
Total	2473	

Exposure to dalbavancin in the Phase 2/3 adult overall safety population is shown by indication and dose in Table 19. Of the disease indications, the majority of patients had ABSSSI, the indication obtained; the smallest proportion had CRBSI. This comprised 1989 patients with ABSSSI, 444 with uSSTI, and 40 with CRBSI.

Of the 2473 patients who received dalbavancin in the Phase 2/3 adult overall safety population, 349 (14.1%) patients received the 1500 mg single-dose-regimen, and 2124 (85.9%) patients received the 2-dose regimen of 1000 mg followed one week later by 500 mg. Of the 1989 dalbavancin patients with ABSSSI, 349 (17.5%) received 1 dose and 1640 (82.5%) received 2 doses.

The safety and effectiveness of dalbavancin when administered for greater than two doses has not been established. Limited experience from longer durations of dosing, however, is available from Study DUR001-104, a phase 1 study in normal volunteers which examined the safety and pharmacokinetics of a single 1000 mg dose followed by 500 mg weekly for 4, 6 or 8 weeks in three cohorts of 8 patients each per cohort. Study DAL-MD-04, a phase 2 study in patients with osteomyelitis assessed the safety and efficacy of 2 doses of 1500 mg weekly for the treatment of osteomyelitis in 70 patients.

Table 19- Extent of Exposure to Dalbavancin by Indication and Dose: Phase 2/3 Adult Overall Safety Population[1]

Dose	Number of Subjects			
	cSSTI (ABSSSI)	uSSTI	CRBSI	TOTAL
Dalbavancin 1 dose [2]	349	0	0	349
Dalbavancin 2 doses	1640	444	40	2124
Dalbavancin Total	1989	444	40	2473

[1] The 3 patients dosed in the VER001-3 study and 70 patients from the DAL-MD-04 study are not included.

[2] One dose is defined as 1500 mg single-dose-regimen for subjects enrolled in DUR001-303 study. The single 1500 mg dose provides the equivalent of 14 days of coverage

Table 20 and Table 21 below show the demographics of the overall safety population. The majority of these patients were <65 years of age, male, and white. However, a sizable minority were 65 or older (14.3%), female (40.5%), or non-white (19.5%).

Table 20- Cumulative subject exposure to dalbavancin from clinical trials by age and sex [1]

Age Range (years)	Number of Subjects		
	Male	Female	Total
0 - <6	56	36	92
6 - <18	83	46	129
18 - <65	1508	946	2454
65 - <75	147	116	263
>= 75	63	122	185
Total	**1857**	**1266**	**3123**

[1] The 3 patients dosed in the VER001-3 study are not included.

Table 21- Cumulative subject exposure to dalbavancin by racial group [1]

Racial Group	Number of Subjects
White	2515
Black or African American	258
Asian	102
American Indian or Alaska Native	18
Native Hawaiian/Other Pacific Islander	3
Other	227
Total	**3123**

[1] The 3 patients dosed in the VER001-3 study are not included.

Although the clinical trial protocols excluded pregnant women and included special measures to prevent pregnancy, three subjects in the dalbavancin clinical programme became pregnant and are discussed in SIV.3.

Baseline creatinine clearance (CrCl) refers to renal status based on estimated calculated CrCl by the Cockcroft-Gault equation measured in mL/min. Baseline hepatobiliary status was considered elevated if either Baseline ALT or AST value is >3×ULN or if Baseline Alkaline Phosphate is >1.5×ULN. These values were not known for all patients in the Phase 2/3 safety populations.

Table 22 below displays the demographic data regarding the renal and hepatic baseline status of subjects in the Phase 2/3 adult overall safety population. Of the 2431 patients with a baseline CrCl, 41 (1.7%) had a value of <30 mL/min, 410 (16.9%) of 30-59 mL/min, 710 (29.2%) of 60-89 mL/min, and 1270 (52.2%) of 90mL/min or more. Of the 2303 patients with a baseline hepatobiliary status as defined in Table 22 it was considered “elevated” in 103 (4.5%) patients and “not elevated” in 2200 (95.5%) patients.

Table 22- Exposure by Special Populations: Baseline Creatinine Clearance and Hepatobiliary Status: Phase 2/3 Adult Overall Safety Population

	Dalbavancin		
Baseline CrCl, n	**1 dose N = 349**	**2 doses N = 2082**	**Total N = 2431**
<30 mL/min	2	39	41
30 to 59 mL/min	51	359	410
60 to 89 mL/min	103	607	710
≥90 mL/min	193	1077	1270
Baseline hepatobiliary*, n	1 dose N=325	2 doses N=1978	Total N=2303
Elevated	9	94	103
Not elevated	316	1884	2200

*if all 3 tests have non-missing Baseline values, the hepatobiliary status is not elevated
CrCl = Creatinine clearance

Exposure to dalbavancin in the paediatric studies is presented in Table 23. Study DUR001-306 enrolled patients with ABSSSI or sepsis. The Phase 1 studies enrolled patients with suspected or confirmed bacterial infections.

Table 23- Extent of Exposure: Paediatric Population

Study number (Phase)	**No. of patients exposed to dalbavancin**	**Age Range**
DUR001-306 (Phase 3)	168	Birth-17 years
DAL-PK-02 (Phase 1)	8	<3 months
A8841004 (Phase 1)	10	12-17 years
DUR001-106 (Phase 1)	34	3 months-11 years
Total	220	

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 24- Key exclusion criteria pertaining to safety are addressed by the contraindications warnings and precautions for use in the summary of product characteristics (SmPC).

Exclusion criteria which will remain as contraindications	
Criteria	Implications for target population
Known hypersensitivity to glycopeptides or comparator drug	Hypersensitivity to the active substance or to any of the excipients

The overall impact of exclusion criteria was considered for the phase 2/3 studies. Exclusion criteria discussed in the table below were either exclusion criteria related to efficacy (to ensure that the appropriate target disease were enrolled, or to avoid confounding of efficacy evaluation), or were related to safety in order to protect trial patients from potential safety risks associated with the investigational product or were GCP related (e.g to ensure that proper follow-up was possible).

Main exclusion criteria across the clinical trial development plan are described in the table below. There were some differences between the safety exclusion criteria used in the Vicuron Phase III studies (VER001-9 and VER001-8), and the Durata Phase III studies (DUR001-301, DUR001-302, and DUR001-303): these changes related to the following safety related exclusion criteria:

Creatinine Clearance: While in the Vicuron trials patients were excluded with a creatine clearance less than 50 ml/min, these patients were allowed in the Durata Phase 3 studies. Dose adjustment was recommended for patients with chronic renal failure if their CrCl <30 mL/min if they are not receiving regularly scheduled renal dialysis.

Oliguria: While in the Vicuron trials oliguria as defined as a urine output of <20 cc/hour averaged over 24 hours was an exclusion criteria, these patients could be included in the Durata Phase 3 studies.

Liver function: While in the Vicuron trials patients were excluded with a known bilirubin >2x the upper limit of normal, these patients could be included in the Durata Phase 3 studies, without dose adjustment.

Active substance abuse: While in the Vicuron trials patient were excluded with active substance abuse, these patients could be included in the Durata Phase 3 studies.

Table 25- Exclusion Criteria In Pivotal Clinical Studies Within The Development Programme

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Known CrCl ≤50 ml/min	Improve clinical trial patient safety until more is known about the effects of renal impairment on the study drug	Although excluded in the Vicuron Phase 2/3 clinical trial program, these patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303, and pharmacokinetic studies were conducted in renally impaired and dialysis patients. Dose adjustment is recommended for patients with chronic renal failure if their CrCl <30 mL/min and they are not receiving regularly scheduled renal dialysis. (SmPC Sections 4.2, 5.2)
Known bilirubin >2x the upper limit of normal	Improve clinical trial patient safety until more is known about the effects of hepatic impairment on the study drug	Although excluded in the Vicuron Phase 2/3 clinical trial program, these patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303, and pharmacokinetic studies were conducted in patients with hepatic impairment. No dose 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 (SmPC sections 4.2, 5.2).
Received a systemically or topically administered antibiotic with a gram-positive spectrum that achieves therapeutic concentrations in the serum or at the site of the ABSSSI within 7 days (Study VER001-9) or 14 days (Studies DUR001-301, DUR001-302, and DUR001-303) prior to randomization	Ensure that efficacy seen in the study is due to the study antibacterial rather than from concomitant/ previous antibacterials	Not relevant, efficacy related exclusion criterion
Known or suspected to have osteomyelitis or septic arthritis	Exclude indications not being studied	Not relevant
Self-limiting infections such as isolated folliculitis and isolated furuncles which have a high cure rate after surgical incision alone	Excludes patients that do not require intravenous antibiotics	Not relevant, efficacy related exclusion criterion
An infection involving a limb with evidence of critical ischemia of an affected limb.	Exclude patients that require a more surgical than medical treatment.	Not relevant.
Concomitant conditions requiring antimicrobial therapy that would interfere with the evaluability of the condition under study	Ensure that efficacy seen in the study is due to the study antibacterial rather than from concomitant/ previous antibacterials	Not relevant

Exclusion criteria which are NOT proposed to remain as contraindications		
Anticipated need for prolonged antibiotic therapy (>14 days)	Exclude indications not being studied, as these are likely to be patients with osteomyelitis or septic arthritis	Not relevant
Neutropenia defined as an absolute neutrophil count <500/mm^3	Subjects with an absolute neutrophil count of less than 500/mm^3, subjects receiving chronic immunosuppressive drugs, and subjects with CD4 counts less than 200/uL were excluded from the clinical trials in order to assess the safety and efficacy profile in the intended patient population without the confounder of immunosuppression.	Based on its mechanism of action, there is no reason to expect that the safety and efficacy of dalbavancin in immunocompromised patients will be any different than that in the general population.
Receiving chronic immunosuppressive drugs, including prednisolone >40 (VER001-9) or >20 (DUR001-301/302/303) mg/day (or equivalent)		
CD4 count known at the time of enrolment to be <200/µL		
Oliguria defined as a urine output of <20 cc/hour averaged over 24 hours	Improve clinical trial patient safety until more is known about the effects of renal impairment on the study drug	Although excluded in the Vicuron clinical trial program, these patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303.
Active substance abuse	Avoids confounding effects of substance abuse on clinical trial safety and efficacy results	Although excluded in the Vicuron clinical trial program, these patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303.
Life expectancy <3 months	Avoids inclusion of patients who are less likely to receive aggressive medical treatment and more likely to have poor outcomes regardless of antibacterial efficacy	Not relevant
Prior exposure to dalbavancin / prior participation in the protocol	Ensure all patient exposures to dalbavancin are unique patients	Not relevant
Causative organism with resistance or insensitivity to vancomycin or comparator drug	Excludes patients with organisms resistant to the comparator antibacterial in the clinical trial	Not relevant
Pregnant or lactating women, or women of childbearing potential not using appropriate contraception	It is not appropriate to include pregnant or lactating women in a clinical trial of an unapproved medication	Section 4.6 of the SmPC indicates the lack of data regarding use of dalbavancin in pregnant or breast-feeding women. As a result, it is recommended that dalbavancin not be used during pregnancy unless the potential expected benefit clearly justifies the potential risk to the foetus, and that decisions on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with dalbavancin should be made taking into account the benefit of breast-feeding to the child and the benefit of dalbavancin to the woman.

SIV.2 Limitations of Adverse Drug Reaction (ADR) detection common to clinical trial development programmes

According to the "rule of threes", uncommon reactions were most likely captured, but some rare reactions might not have been detected with the current subject exposure. Dalbavancin is not intended to be used for longer than 2 weeks (2 doses). Although dalbavancin has a long half-life, few late onset adverse reactions were observed. Two phase 3 studies followed the patients for 70 days and one phase 2 study followed patients for 1 year. The number of patients included in these studies is sufficient to capture only common adverse reactions with such a late onset (up to 2 months after last dose).

Table 26- Limitations to Detect Adverse Reactions in Clinical Development Programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are uncommon or rare (it may be appropriate to choose other ADR frequencies)	A total of 3097 unique subjects received IV dalbavancin in the Phase 1, 2, and 3 studies.	Using the "rule of 3" for detection of rare adverse events, ADRs with a frequency greater than 1 in 960 (0.10%) could be detected if there were no background incidence. Thus, the clinical trial programme would have detected the majority of uncommon adverse events, but rare adverse events may not be detected.
Prolonged exposure and cumulative effect	Although no apparent accumulation was observed with multiple weekly dosing of dalbavancin up to 8 weeks, it was only studied in 18 healthy subjects (DUR001-104).	Dalbavancin is not proposed to be used for more than 2 weeks, but prolonged exposure might occur in the context of off label use.
Long latency	Most of the phase 2/3 studies followed the patients up for at least 39 days. In study VER001-9, 571 dalbavancin treated subjects were followed for 39 days. In the Phase 3 Studies DUR001-301 and DUR001-302, 593 patients exposed to dalbavancin were followed up to Day 70. In study DAL-MD-04, 70 patients exposed to dalbavancin were followed up to 1 year.	Dalbavancin has a long half-life (beta half-life of 5-7 days and a terminal half-life of approximately 346 hours). Some late onset skin reactions were noted, but none were clearly attributed to dalbavancin. Duration of skin related ADRs (including rashes) was similar between dalbavancin and comparator treated patients However, uncommon or rarer very late onset adverse reactions may not have been detected.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Children

Children less than 18 years of age were not included in the adult clinical programme with the exception of two 16 year old subjects who were enrolled in VER001-4 trial. A paediatric investigation plan was agreed with the PDCO to assess ABSSSI in paediatrics prior to obtaining the marketing authorization in Europe.

Ten adolescents age 12 to 16 years old were enrolled in the PK study A8841004, and 34 subjects age 3 months to 11 years old were enrolled in study DUR001-106. Eight subjects (neonates to infants <3 months) with suspected or confirmed bacterial infection were enrolled in PK study DAL-PK-02.

A total of 198 subjects with ABSSSI from birth to age <18 years old were enrolled in Study DUR001-306.

Study DUR001-306 assessed the safety and efficacy of dalbavancin for the treatment of ABSSSI in children, from birth to 17 years (inclusive). Table 27 and Table 28 provide a comparison of frequency of adverse events seen in the Phase 3 study by age groups in dalbavancin and comparator-treated subjects, respectively. Overall, a low proportion of subjects experienced a treatment-emergent adverse event (TEAE) (8.9% of subjects in dalbavancin single-dose arm, 9.0% of subjects in the dalbavancin two-dose arm, and 3.3% of subjects in the comparator arm). At least 1 subject in Cohorts 1 through 4 experienced a TEAE in each of the dalbavancin treatment arms, with the exception of subjects in the 2-dose dalbavancin arm in Cohort 4. In Cohort 5 (which only received the single-dose treatment), the TEAEs occurred in the dalbavancin single-dose group. The 1 TEAE in the comparator arm was reported in the 2-year to <6-year age cohort. No treatment-related TEAEs were reported in the study. Three serious adverse events (SAEs) were reported, all in the dalbavancin single-dose arm; with 1 each in the birth to <3-month, 3-month to <2-year, and 12-year to 17-year cohorts. There were no treatment-related SAEs, no AEs leading to discontinuation of study intervention or study, and no SAEs leading to death.

Table 27- Frequency of adverse events by age in dalbavancin-treated paediatric patients – Study DUR001-306

Age in years	Age Group								
	Age Birth - <3 months	Age 3 months - <2 years		Age 2 years to <6 years		Age 6 years - <12 years		Age 12 years – 17 years	
	Dalbavancin Single-Dose (N=9) n/N (%)	Dalbavancin Single-Dose (N=9) n/N (%)	Dalbavancin Two-Dose (N=8) n/N (%)	Dalbavancin Single-Dose (N=18) n/N (%)	Dalbavancin Two-Dose (N=17) n/N (%)	Dalbavancin Single-Dose (N=25) n/N (%)	Dalbavancin Two-Dose (N=24) n/N (%)	Dalbavancin Single-Dose (N=29) n/N (%)	Dalbavancin Two-Dose (N=29) n/N (%)
Number of Patients Who Experienced at Least One:									
AE	2/9 (22.2)	3/9 (33.3)	4/8 (50.0)	1/18 (5.6)	1/17 (5.9)	1/25 (4.0)	1/24 (4.2)	1/29 (3.4)	2/29 (6.9)
TEAE	2/9 (22.2)	3/9 (33.3)	4/8 (50.0)	1/18 (5.6)	1/17 (5.9)	1/25 (4.0)	0	1/29 (3.4)	2/29 (6.9)
Treatment-related TEAEs	0	0	0	0	0	0	0	0	0
Treatment-emergent Serious TEAE	1/9 (11.1)	1/9 (11.1)	0	0	0	0	0	1/29 (3.4)	0
Treatment-related Treatment-emergent SAEs	0	0	0	0	0	0	0	0	0
AEs leading to study treatment discontinuation	0	0	0	0	0	0	0	0	0
AEs leading to study discontinuation	0	0	0	0	0	0	0	0	0
Treatment-emergent SAEs leading to death	0	0	0	0	0	0	0	0	0

Table 28- Frequency of adverse events by age in comparator-treated paediatric patients – Study DUR001-306

Age in years	Age Group				
	Age Birth - <3 months (N=0) n/N (%)	Age 3 months - <2 years (N=3) n/N (%)	Age 2 years to <6 years (N=10) n/N (%)	Age 6 years - <12 years (N=11) n/N (%)	Age 12 years – 17years (N=6) n/N (%)
Number of Patients Who Experienced at Least One:					
AE	-	0	1/10 (10.0)	0	0
TEAE	-	0	1/10 (10.0)	0	0
Treatment-related TEAEs	-	0	0	0	0
Treatment-emergent Serious TEAE	-	0	0	0	0
Treatment-related Treatment-emergent SAEs	-	0	0	0	0
AEs leading to study treatment discontinuation	-	0	0	0	0
AEs leading to study discontinuation	-	0	0	0	0
Treatment-emergent SAEs leading to death	-	0	0	0	0

Table 29 provides the most common reported treatment-related TEAE (>2% of subjects in either treatment group) for the five different age groups. TEAEs that occurred in more than 1 subject in any treatment arm were pyrexia and cough (each in 2 subjects in the dalbavancin two-dose arm), nasopharyngitis (1 subject in the dalbavancin single-dose arm and 1 in the comparator arm), and postoperative anemia (1 subject in the dalbavancin two-dose arm and 1 in the comparator arm). All other TEAEs occurred in no more than 1 subject in any treatment arm.

Table 29- Common (>2% in any Treatment Group) Treatment-Related Adverse Events by age group of paediatric patients – Study DUR001-306

	Treatment Group		
	Dalbavancin Single-Dose n/N (%)	Dalbavancin Two-Dose n/N (%)	Comparator n/N (%)
Age group: 3 months - <2 years old	1/9 (11.1)	3/8 (37.5)	0
Pyrexia	0	2/8 (25.0)	0
Nasopharyngitis	1/9 (11.1)	0	0
Anaemia postoperative	0	1/8 (12.5)	0
Cough	0	1/8 (12.5)	0
Age group: 2 years - <6 years old	0	1/17 (5.9)	1/10 (10.0)
Nasopharyngitis	0	0	1/10 (10.0)
Anaemia postoperative	0	0	1/10 (10.0)
Cough	0	1/17 (5.9)	0

In the Phase 1 Study DAL-PK-02 which enrolled preterm neonates to infant ages <3 months with suspected or confirmed bacterial infection, 35 TEAEs were reported for 6 subjects, all in Cohort 1 (>28 days to <3 months). The majority of TEAEs were mild or moderate in severity. The most commonly reported TEAEs were pyrexia (3 [37.5%] subjects) and procedural pain (2 [25.0%] subjects). All other TEAEs were reported as single instances. One subject experienced treatment-emergent SAEs (necrotizing colitis and hydrocephalus). There were no treatment-related SAEs and no SAEs leading to death.

In the Phase 1 Study A8841004 which enrolled subjects from 12 to 17 years of age with bacterial infections, 9 subjects had TEAEs. The event of headache, experienced by 1 participant in each dose group, was the only AE to be experienced by more than 1 participant. One SAE, mild ileus, was reported from 1 subject receiving dalbavancin 15 mg/kg. There were no treatment-related SAEs and no SAEs leading to death.

In the Phase 1 Study DUR001-106 which enrolled hospitalized children aged 3 months to 11 years with bacterial infections, 36 TEAEs were reported during the study. There were a total of 9 TEAEs in Cohort 1 (6 to 11 years of age), 23 in Cohort 2 (2 to <6 years of age), and 4 in Cohort 3 (3 months to <2 years of age), occurring in 6 (54.4%), 9 (75.0%), and 4 (36.4%) subjects, respectively. The most commonly reported TEAEs (2 subjects overall) were acoustic simulation tests abnormal, acute respiratory failure, audiogram abnormal, dermatitis diaper, and pruritus. All other TEAEs were reported as single instances. Five subjects had SAEs of abdominal pain, arthralgia, device-related sepsis, abdominal abscess, and acute respiratory failure. There were no treatment-related SAEs and no SAEs leading to death.

Overall, dalbavancin has been well tolerated in the paediatric population and there were no unexpected AEs in paediatric subjects relative to the known safety profile of dalbavancin in adult subjects.

Elderly

Approximately 15% of adult patients on dalbavancin were older than 65 (Table 20). Table 30 and Table 31 provide comparison of frequency of adverse events seen in phase 2/3 studies by age groups in dalbavancin and comparator treated subjects, respectively.

In the phase 2/3 adult safety population analysis in both the dalbavancin and comparator groups, the numbers of subjects ≥65 years of age (403 and 229 subjects, respectively) were smaller than of subjects <65 years of age (2070 and 995 subjects, respectively). However, the incidences of subjects who had ≥1 TEAE were similar between age groups. Among subjects ≥65 years of age, 43.4% of dalbavancin treated subjects and 47.2% of comparator-treated subjects had ≥1 TEAE. Among <65 years of age, 36.9% of dalbavancin-treated subjects and 46.7% of comparator-treated subjects experienced ≥1 TEAE. There were fewer subjects each in the categories of ≥65 to <75 years, ≥75 to <85 years and ≥85 years to draw any meaningful conclusions, but overall the incidences of subjects who had ≥1 TEAE were similar between age groups in both the dalbavancin and comparator groups. No trend of increasing incidence of TEAEs by increasing age was observed in either treatment group.

In general, incidences and types of laboratory abnormalities during treatment and at End of Treatment (EOT) and Test Of Cure (TOC) in the phase 2/3 adult overall safety population did not increase in subjects ≥65 years of age in comparison to subjects <65 years of age. The pharmacokinetics of dalbavancin are not significantly altered with age, no dose adjustment is needed in the elderly. The elderly

were adequately represented in the dalbavancin clinical programme, and no adverse events of special concern have been identified.

Table 30- Frequency of adverse events by age in dalbavancin-treated adult patients – Phase 2/3 Adult Overall Safety Population

	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	2070/2473 (83.7)	230/2473 (9.3)	158/2473 (6.4)	15/2473 (0.6)
Number of Patients Who Experienced at Least One:				
AE	790/2070 (38.2)	97/230 (42.2)	76/158 (48.1)	9/15 (60.0)
TEAE	763/2070 (36.9)	92/230 (40.0)	74/158 (46.8)	9/15 (60.0)
Serious TEAE	85/2070 (4.1)	21/230 (9.1)	15/158 (9.5)	0
Treatment-Emergent SAE Leading to Death	5/2070 (0.2)	3/230 (1.3)	4/158 (2.5)	0
Discontinuation of Study Drug due to TEAE	40/2070 (1.9)	10/230 (4.3)	2/158 (1.3)	1/15 (6.7)
AE Related to falling	3/2070 (0.1)	2/230 (0.9)	1/158 (0.6)	0
Cardiovascular Events	20/2070 (1.0)	11/230 (4.8)	11/158 (7.0)	1/15 (6.7)
Cerebrovascular Events*	0	1/230 (0.4)	1/158 (0.6)	0
Infections and Infestations	194/2070 (9.4)	24/230 (10.4)	23/158 (14.6)	4/15 (26.7)
Nervous system Disorders	147/2070 (7.1)	17/230 (7.4)	8/158 (5.1)	2/15 (13.3)

Table 31- Frequency of adverse events by age in comparator-treated adult patients – Phase 2/3 Adult Overall Safety Population

	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	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)
Cardiovascular Events	24/995 (2.4)	8/126 (6.3)	3/90 (3.3)	0
Cerebrovascular Events*	1/995 (0.1)	1/126 (0.8)	0	0
Infections and Infestations	143/995 (14.4)	12/126 (9.5)	15/90 (16.7)	5/13 (38.5)
Nervous system Disorders	87/995 (8.7)	4/126 (3.2)	6/90 (6.7)	3/13 (23.1)

Table 32 provides the most common reported treatment-related TEAE (>2% of patients in either treatment group) for the four different age groups. The treatment-related TEAEs that occurred in >2% subjects in either the dalbavancin or comparator groups were in subjects <65 years of age; diarrhoea (3.1% and 5.8% respectively), nausea (4.7% and 7% respectively), headache (4% and 5.7% respectively), and vomitting (2.3% and 3.2% respectively) in subjects ≥65 to <75 years of age; diarhoea (0.8% and 3.3% respectively), GGT increased (0.8% and 2.2% respectively) and oral candidiasis (0.8% and 3.3% respectively) in subjects aged ≥75 to <85 years. There were only 13 subjects each in the dalbavancin and comparator groups that were ≥85 years of age and for this group, candidiasis was the only treatment-related TEAE that occurred in >1 subject (none in the dalbavancin group and 2 in the comparator group).

Table 32- Common (>2% in any Treatment Group) Treatment-Related Adverse Events by age group – Phase 2/3 Adult Overall Safety Population

	Treatment Group	
	Dalbavancin n/N (%)	Comparator n/N (%)
Age group: <65, N1	2070/2473 (83.7)	995/1224 (81.3)
Nausea	53/2070 (2.6)	37/995 (3.7)
Diarrhoea	41/2070 (2.0)	36/995 (3.6)
Pruritus	11/2070 (0.5)	22/995 (2.2)
Age group: >=65 - <75, N1	230/2473 (9.3)	126/1224 (10.3)
Diarrhoea	6/230 (2.6)	5/126 (4.0)
Nausea	5/230 (2.2)	3/126 (2.4)
Thrombocytopenia	0	3/126 (2.4)
Age group: >=75 - <85, N1	158/2473 (6.4)	90/1224 (7.4)
Diarrhoea	1/158 (0.6)	3/90 (3.3)
Gamma-glutamyltransferase increased	1/158 (0.6)	2/90 (2.2)
Oral candidiasis	1/158 (0.6)	3/90 (3.3)
Age group: >=85, N1	15/2473 (0.6)	13/1224 (1.1)
Blood lactate dehydrogenase increased	1/15 (6.7)	0
Blood uric acid increased	1/15 (6.7)	0
Nausea	1/15 (6.7)	0

Gender

Dalbavancin subjects in the adult overall safety population were 58% male and 42% female. In the Phase 2/3 adult safety population, the incidence of TEAEs was higher for female patients (41.1% for patients who received any dose of dalbavancin and 51.7% for patients who received comparator) compared to male patients (35.8% and 43.3% of patients, respectively). For female patients frequently reported TEAEs generally had a lower incidence for patients who received dalbavancin than for comparator. There were no notable differences in the frequencies or types of laboratory abnormalities by gender during treatment and at EOT and TOC in the phase 2/3 adult safety population. Clinically significant gender-related differences in dalbavancin pharmacokinetics have not been observed in healthy subjects or in patients

with infections (SmPC 5.2). Both genders were adequately represented in the dalbavancin clinical programme and no adverse events of special concern have been identified.

Pregnant or breast feeding women

In clinical trials with dalbavancin, pregnant or lactating females, or females of childbearing potential not using an acceptable method of birth control were specifically excluded.
Due to short term use, new pregnancies occurring while on dalbavancin are less likely than with chronic therapies. The safety database contains 3 pregnancy reports from the 21 clinical trials: one pregnancy, one positive serum pregnancy test and one ectopic pregnancy were reported for dalbavancin patients which are described below. There have been no additional pregnancies, nor positive pregnancy tests, in Study DUR001-303 or subsequent studies as of DLP of 29 August 2019.

Subject [redacted] entered Study VER001-9 based on a negative urine pregnancy test and menstruation at screening. The subject's serum pregnancy test result was found to be positive during infusion of the first dose of study medication. Study medication was immediately discontinued. The subject received only 7.2 mL of the infusion. A repeat serum pregnancy test on Day 10 was negative and the subject was still menstruating. Because this positive serum pregnancy test was drawn at Baseline prior to infusion of study drug, it was considered a Baseline event and was not tabulated as an AE leading to withdrawal from study medication.

Subject [redacted], a [redacted] year [redacted] female, had an IUD in place at the time of the study entry (since [redacted] 2009). She received dalbavancin 1000 mg IV on [redacted] 2011. During the scheduled study exit procedures on [redacted], her serum ßhCG was elevated (15.98 mIU/mL); the elevation was confirmed on [redacted] (21.72 mIU/mL) and [redacted] (36.55 mIU/mL). A transvaginal pelvic ultrasound on [redacted] confirmed an ectopic pregnancy in the fallopian tube. The subject's pregnancy was terminated with IM methotrexate on [redacted] and her serum ßhCG rapidly returned to normal. The ectopic pregnancy was considered unrelated to dalbavancin by the investigator.

Subject [redacted], a [redacted] year female (91 kg) received 2 doses of dalbavancin as per protocol. Approximately 3 weeks after the second dose of dalbavancin a positive pregnancy test was reported. At that time an ultrasound was negative, but a follow up ultrasound done 18 days later showed a viable intrauterine pregnancy with estimated gestational age of 6 weeks and 6 days. At
39 weeks a baby was born, no details were provided on the status of the child except the birth weight: 5 pounds and 14 oz.

Subjects who are breastfeeding are commonly excluded from clinical trials. Available pharmacokinetic data in animals have shown that dalbavancin crosses the placenta and is excreted into milk in rats.

The SmPC recommends dalbavancin should not be used during pregnancy unless clearly necessary, i.e., if the potential expected benefit clearly justifies the potential risk to the foetus. It also recommends that a decision on whether to continue or discontinue breastfeeding or to continue or discontinue therapy with dalbavancin should be made taking into account the benefit of breast-feeding to the child and the benefit of dalbavancin to the woman.

Patients with hepatic impairment

In three of the four pivotal studies patients with hepatic impairment were not excluded.
Of the 2473 dalbavancin-treated patients with a baseline hepatobiliary status as defined in Table 22, it was considered "elevated" in 103 (4.2 %) patients and "not elevated" in 2200 (89%) patients.

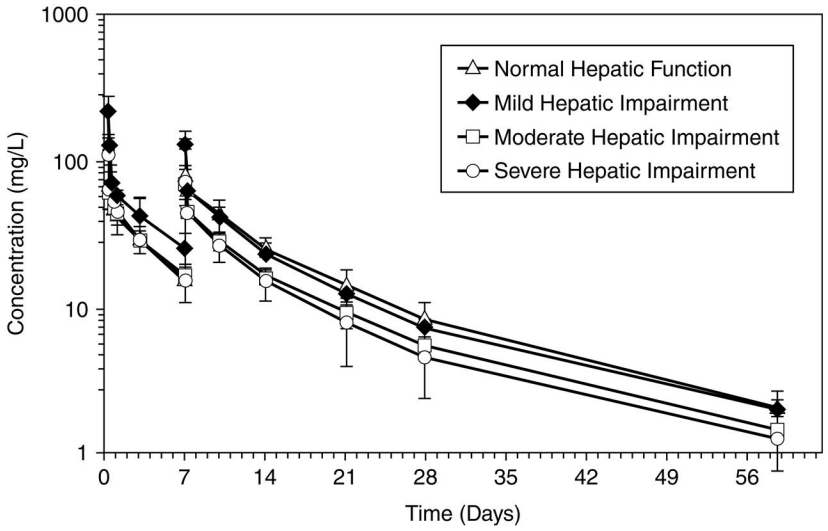
The majority of those subjects with elevated baseline hepatobiliary values were <65 years of age (82 subjects [79.6%] for total dalbavancin and 63 subjects [82.9%] for comparator), with slight difference in gender (51.5% male, 48.5% female for total dalbavancin and 57.9% male and 42.1% female for comparator). Similar demographic percentages were seen in subjects with non-elevated baseline hepatobiliary status.

In the phase 2/3 adult overall safety population, the incidences of subjects with treatment-related TEAEs were similar in subjects who had elevated baseline hepatobiliary values and in those who did not. Among subjects with elevated baseline hepatobiliary values, 21 (20.4%) dalbavancin-treated subjects and 14 (18.4%) comparator-treated subjects experienced ≥1 treatment-related TEAE. Among subjects with non-elevated baseline hepatobiliary values, 332 (15.1%) dalbavancin-treated subjects and 226 (21.1%) comparator-treated subjects experienced ≥1 treatment-related TEAE. Potentially clinically significant laboratory results and greater adverse transitions in hepatobiliary parameters were more commonly reported in subjects who had elevated hepatobiliary values at baseline than in subjects with non-elevated baseline hepatobiliary values.

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 (Study VER001-12). Dalbavancin was well tolerated in this population; there were no deaths, life-threatening AEs, or SAEs.

The exposure to dalbavancin for subjects with normal hepatic function and subjects with mild hepatic impairment was comparable. There was significant overlap in concentrations through the profiles across groups, with mean concentrations remaining above 10 mg/L in all groups through the intended treatment duration of 14 days. There was also overlap in drug exposure across the groups (Figure SIV.3-1) Even with a decrease in mean exposure, subjects with severe hepatic impairment still had a drug exposure through the relative treatment period (14 days) that exceeded parameters required for successful treatment of their skin infection. The SmPC states that no dose adjustment of dalbavancin is recommended for patients with mild hepatic impairment (Child Pugh A) and that 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. The use of dalbavancin in this subpopulation is included in the RMP as missing information.

Figure SIV.3-1 **Mean (± SD) Dalbavancin Plasma Concentration-Time Profiles following Administration of 1000 mg Dalbavancin Day 1 and 500 mg Dalbavancin on Day 8 in Subjects with Mild Hepatic Impairment, Moderate Hepatic Impairment, Severe Hepatic Impairment, or Normal Hepatic Function**



Patients with hepatic disorders were adequately represented in the dalbavancin clinical programme and no adverse events of special concern in hepatic impaired patients have been identified.

Patients with renal impairment

In the three phase 3 trials (DUR001-301, DUR001-302, DUR001-303) patients with renal impairment were not excluded. Two phase I studies have been performed in renal impaired patients. One phase I study was in subjects with mild/moderate renal impairment (Study VER001-13), and one study in subjects with severe renal impairment and end-stage renal disease (ESRD) subjects (StudyVER001-11).

Table 33 shows the percent of subjects with at least one AE by baseline CrCl and dose of study drug. Of the phase 2/3 dalbavancin and comparator patients, similar percentages had Baseline CrCl values within each of the CrCl categories. The percent of subjects with at least one AE was roughly similar amongst the 2 treatment groups within baseline CrCl category; patients with a baseline CrCl below 60 mL/min tended to have a higher percent of AEs.

Table 33- Overview of Treatment-Emergent Adverse Events (TEAE) by Creatinine Clearance Category—Phase 2/3 Adult Overall Safety Population

	Phase 2/3 Adult Overall Safety Population	
	Dalbavancin (N=2473)	**Comparator (N=1224)**
Number of subjects, N (%)		
<30 mL/min	41 (1.7)	21 (1.7)
30 to 59 mL/min	410 (16.6)	225 (18.4)
60 to 89 mL/min	710 (28.7)	344 (28.1)
≥90 mL/min	1270 (51.4)	607 (49.6)
Number of subjects with ≥1 TEAE, n/N (%)		
<30 mL/min	17/41 (41.5)	9/21 (42.9)
30 to 59 mL/min	172/410 (42.0)	117/225 (52.0)
60 to 89 mL/min	259/710 (36.5)	162/344 (47.1)
≥90 mL/min	465/1270 (36.6)	272/607 (44.8)

Source: ISS table 1.1, 1.3, 4.2.11

In the Phase 2/3 adult safety population, the incidence of renal adverse events was similar between patients treated with dalbavancin or comparator agents (1.7% and 1.8% respectively). As demonstrated in Table 34 below no Drug-Related Treatment-Emergent SAE were observed in subjects with baseline CrCl <30 mL/min in the dalbavancin treatment group, and were only rarely seen in subjects with higher baseline CrCls and were similar between dalbavancin-treated and comparator-treated subjects.

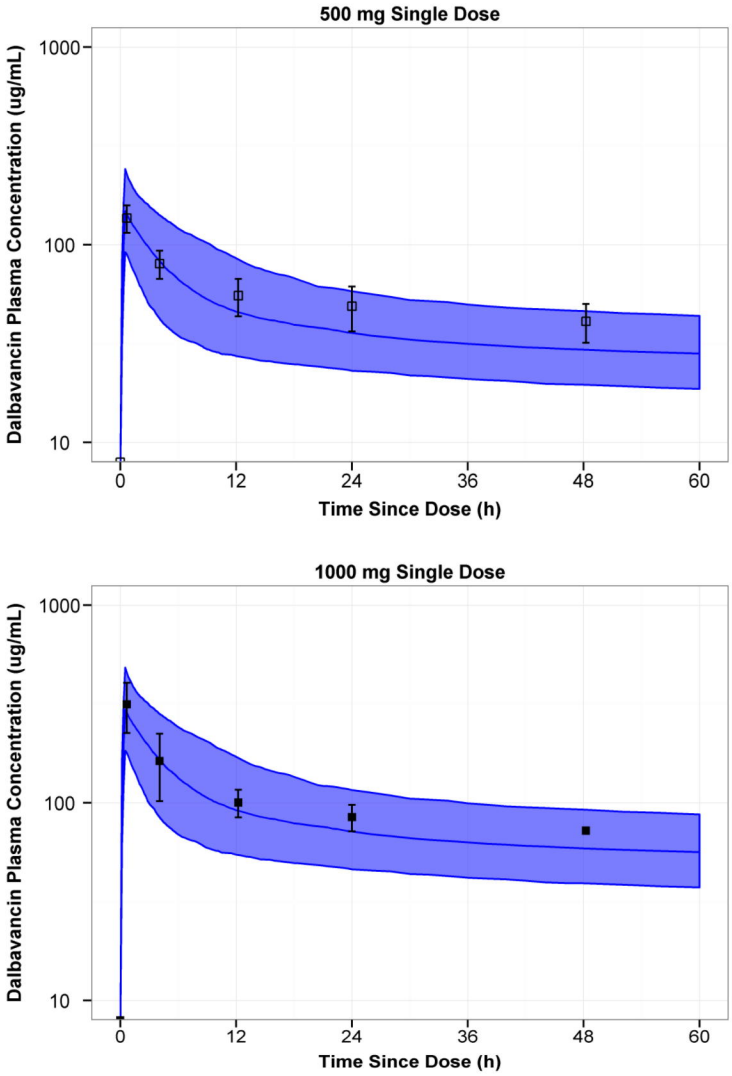
Table 34- Adverse events in Adults Patients with and without severe renal impairment – Phase 2/3 Adult Safety Population

	CrCl <30 mL/min N=62		**CrCl ≥30 mL/min N=3566**	
Number of Patients Who Experienced at Least One	Dalbavancin n/N(%)	Comparator n/N(%)	Dalbavancin n/N(%)	Comparator n/N(%)
-TEAE	17/41 (41.5)	9/21 (42.9)	896/2390 (37.5)	551/1176 (46.9)
-Drug-Related TEAE	5/41 (12.2)	2/21 (9.5)	359/2390 (15.0)	240/1176 (20.4)
-Serious TEAE	6/41 (14.6)	4/21 (19.0)	113/2390 (4.7)	73/1176 (6.2)
-Drug-Related Treatment-Emergent SAE	0	1/21 (4.8)	5/2390 (0.2)	8/1176 (0.7)

The pharmacokinetics of dalbavancin were evaluated in 28 patients with varying degrees of renal impairment and 15 matched control subjects with normal renal function. There were no deaths, and no subject prematurely withdrew from the study due to AEs, and only two SAEs were reported, both of which were assessed as unrelated.

A comparison of the observed mean dalbavancin concentration-time profiles from Study VER001-11 to the population model-predicted dalbavancin concentration-time profile for patients with CLcr below 30 mL/min is provided in Figure SIV.3-2. Considering that the observed data are comprised of ten subjects enrolled in a Phase 1 study and that the population PK model was developed using data from infected patients, these plots indicate that the mean predicted profile from the population PK model adequately captures the mean profile observed in subjects with severe renal impairment. The proposed adjustment in dosing for patients with renal insufficiency was made in order to insure that the AUC for these patients would be similar to that of patients with normal renal function. While the $AUC_{0\text{-}inf}$ is approximately 90% higher, this is occurring mostly because of the prolonged 'tail' of exposure at a time when the actual serum levels of dalbavancin are quite low. Based on an AUC/MIC target attainment model, efficacy thresholds would be reached more frequently, potentially of clinical value in patients who, because of this underlying comorbidity, might otherwise have a lower likelihood of achieving clinical success.

Figure SIV.3-2 Comparison of model-predicted concentrations to the mean concentration-time profiles observed in patients with severe renal impairment (VER001-11)



In two of the three pivotal studies patients with renal impairment were not excluded were dose adjusted when CrCl values were below 30 mL/min.

Patients with renal disorders were adequately represented in the dalbavancin clinical programme and no adverse events of special concern have been identified.

Patients with other relevant comorbidity

Diabetes Mellitus

The population studies in the dalbavancin clinical programme are representative of the ABSSSI population with regard to Diabetes Mellitus.

In the phase 3 studies in adult patients (VER001-9, VER001-16, VER001-8, DUR001-301, DUR001-302 and DUR001-303), a substantial percentage of patients had a history of diabetes mellitus (ranging from 9.4% to 36.7% across treatment groups). The prevalence of patients with a history of diabetes mellitus was higher in the patients enrolled in Study VER001-9 compared to those enrolled in Study DUR001-301,Study DUR001-302, and study DUR001-303:

- In study VER001-9 study (ITT population) the incidence of patients with a history of diabetes mellitus was similar in each treatment regimen. Diabetes mellitus was reported at study entry in a total of 199 subjects (23.3 %): 139 subjects (24.3%) in the dalbavancin group and 60 subjects (21.2 %) in the linezolid group.

- In the 301 study (ITT population) diabetes mellitus was reported as medical history in 43 (14.9%) dalbavancin-treated subjects and 30 (10.5%) vancomycin/linezolid-treated subjects. The criteria for pre-diabetes (defined as fasting blood glucose >5.6 and <7.0 mmol/L) was met by 66 (22.9%) subjects in the dalbavancin treatment group and 76 (26.7%) patients in the vancomycin/linezolid group and the criteria for diabetes mellitus with fasting blood glucose >7 mmol/L was met by 47 (16.3%) subjects in the dalbavancin treatment group and 42 (14.7%) subjects in the vancomycin/linezolid group.

- In the 302 study (ITT population), the incidence of patients with a history of diabetes mellitus was similar in each treatment group (35 [9.4%] patients) than in the vancomycin/linezolid treatment group (62 [16.8%] patients; P=0.003). However, when fasting blood glucose results at Baseline were analyzed, 110 (14.9%) patients met the criteria for diabetes mellitus with fasting blood glucose >7 mmol/L and another 171 (23.1%) patients met the criteria for pre-diabetes with a fasting glucose measurement >5.6 mmol/L and <7.0 mmol/L. Using these data, the proportion of patients with diabetes or pre-diabetes was similar in each treatment regimen (143/371 [38.5%]in the dalbavancin treatment group and 138/368 [37.5%] in the vancomycin/linezolid treatment group).

- In the 303 study (ITT population), the incidence of patients with a history of diabetes mellitus was similar in each treatment group (38 (10.9%) patients on dalbavancin single-dose and 42 (12%) patients on dalbavancin two-dose group).

Despite the fact that ABSSSI caused by diabetic foot were excluded in the Durata Phase 3 trials, patients with Diabetes Mellitus were adequately represented in the dalbavancin clinical programme and no adverse events of special concern have been identified.

In studies DUR001-301 and DUR001-302, the incidences of subjects with AEs potentially related to effects on glucose homeostasis were low in the dalbavancin and comparator treatment groups, and of similar frequency, type, severity, and relationship to treatment. Only a few events were considered by the investigator to be related to study drug. The AEs considered possibly or probably related to treatment with dalbavancin (or the relationship was missing) in 0.1 and 0.2% of subjects were hyperglycaemia and hypoglycaemia, respectively. The AEs considered possibly or probably related to treatment with a comparator (or the relationship was missing), each of which were reported in 0.2% of subjects, included: blood glucose increased, hypoglycaemia, and hyperglycaemia.

Serious adverse events potentially related to effects on glucose homeostasis were uncommon in the dalbavancin and comparator groups (one (0.1%) in each group) and all were assessed by the investigators as unrelated to study drug. The frequencies of glucose-related laboratory abnormalities (both hyperglycemia and hypoglycemia) were similar in dalbavancin- and comparator-treated subjects. Additionally, confounding factors likely to contribute to the development of dysglycaemia were present in

the majority of the clinical cases of laboratory hypoglycemia or hyperglycemia. These factors included diabetes mellitus, poor glycemic control, obesity, infection, cancer, malnourishment, or concomitant medications. Based on these data, there is no evidence to suggest a treatment-related effect of dalbavancin on glucose homeostasis.

In study DUR001-303, the incidence of subjects with AEs potentially related to effects on glucose homeostasis were low in both the single and two-dose regimen treatment groups, and of similar frequency, type, severity, and relationship to treatment. There were no events considered by the investigator to be related to study drug. Serious adverse events potentially related to effects on glucose homeostasis were uncommon (one (0.3%) SAE of hyperglycemia in the single dose treatment group) and was assessed by the investigators as unrelated to study drug. The DUR001-303 study data does not suggest a treatment-related effect of dalbavancin on glucose homeostasis.

Peripheral Arterial disease

Peripheral arterial disease (PAD) is a complicated comorbidity because it is associated so closely with diabetes mellitus and with anatomical restriction of blood flow within the arterial system. The patients with anatomical restriction are excluded by convention from the trials in this indication due to the focus on surgical intervention in patients with PAD. Therefore the number (percentage) of patients enrolled in the ABSSSI programme was low but similar between treatment groups: In Study VER001-9, 61 (10.7%) dalbavancin-treated patients and 18 (6.4%) comparator treated patients had a history of vascular disease; in the 301 /302 studies (ITT population) 3 (0.5%) in dalbavancin treated subjects and 7 (1.1%) in vancomycin/linezolid treated subjects had a history of peripheral arterial disease. In addition, diabetes mellitus and pre-diabetes was prevalent in approximately half of the patients and this is a common co-morbidity of PAD (see Section SI.3, Important co-morbidities found in the target population).

Immunocompromised patients

The adult Phase 2/3 clinical programme excluded patients with neutropenia defined as an absolute neutrophil count <500/mm3, patients receiving chronic immunosuppressive drugs, including prednisolone >40 mg/day (VER001-9) or >20 mg/day (DUR001-301/302) (or equivalent), and patients with CD4 count known at the time of enrolment to be <200/μL.

There is no reason that dalbavancin would be less tolerated or less effective in the immune-compromised population.

The limitations of the clinical data are discussed in section 4.4 of the SMPC and includes severely immunocompromised patients.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

The Durata phase 3 studies were intentionally set up to include the severe ABSSSI patient population, with significant comorbidity. This was reflected by the fact that there was considerable comorbidity (see above) as reflected in the incidence of fever in over 80% of all patients and evidence for Systemic Inflammatory Response Syndrome (SIRS) in over one third of enrolled patients in the DUR001-301, DUR001-302, and DUR001-303 trials.

Patients of different racial and/or ethnic origin

In the phase 2/3 adult safety population, the majority of patients (78.1%) were white. A significant number of black or African American patients (8.0%), Asian patients 2.0%), and patients of other race (11.9%) were also included in this population. A pharmacokinetic study included 15 Japanese healthy volunteers (DUR001-103) and a lung epithelial lining fluid study included 37 Japanese healthy volunteers (DUR001-109).

In the Phase 3 paediatric Study DUR001-306, the majority of subjects were white (88.5%). A significant number of Black or African American subjects (5.2%), American Indian Alaska Native subjects (3.1%), subjects of multiple race (2.1%), and Asian subjects (1.0%) were also included in this population. In the Phase 1 Study DAL-PK-02, 7 subjects (87.5%) were white and 1 subject (12.5%) was of multiple race. In the Phase 1 Study A8841004, 5 subjects were white (50.0%) and 5 subjects were black (50.0%). In the Phase 1 Study DUR001-106, 30 subjects (83.3%) were white and 6 subjects (16.6%) were black or African American.

Patients of various racial or ethnic background were adequately represented in the dalbavancin clinical program.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

Dalvance (Durata's US brand of dalbavancin) was approved by the FDA on 23 May 2014, and launched on 18 July 2014. Xydalba was authorised across the European Economic Area on 19 February 2015 and first EEA country launched was Austria in September 2015. Information in this section covers the period from 18 July 2014 to 21 June 2021.

SV.1 Post-authorisation exposure

SV.2.1 Method used to calculate exposure

The patient number is estimated based on direct number of vials ordered by hospitals and a combination of IMS Drug Distribution Data (DDD), ANDA, and Trade Sales data. It was assumed that each patient has used 3 vials of 500mg (1500mg total).

SV.2.2 Exposure

Cumulatively through the DLP, 21 June 2021, the total number of dalbavancin vials distributed is 523,769 vials which equates to 174,589 patients.

There have been [redacted] vials distributed in the US and 147,110 vials distributed in rest of world. Exposure by age and gender are provided in Table 35 below and are estimated using AMR Hospital Antibiotic Market Guide MAT data. AMR data covers hospitals and allows for applying the % factor for patient age and gender to overall patient exposure numbers segmented by age and gender. The assumption is the breakdown by age and gender in other channels (i.e. outpatient facilities) will be consistent with what AMR reports. AMR data is audit based and includes random samples of clinical profiles of antibiotic patients from a range of hospitals across the US.

Table 35- Cumulative Exposure to Dalbavancin

	Sex [a]		*Age* [a]			*Region* [c]		
	M	*F*	*0-17*	*18-64*	*>65*	*USA*	*EEA*	*ROW*
Cumulative exposure								
Vials sold	250,548	126,222	0	282,662	93,774	[redacted]	135,565	11,545
Estimated exposure [b]	83,516	42,074	0	94,221	31,258		45,188	3,848

[a] Information available from US data only. Data is estimated based on AMR Hospital Antibiotic Market Guide.

[b] Exposure is calculated by estimating that each patient received 3 vials. It is assumed that each patient received the recommended 1500 mg dose from 3 vials of 500 mg each.

[c] USA data is based on Trade Sales data. EU data is based on sales data provided by MAH partners, Angelini and Correvio

.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for drug abuse with dalbavancin is considered to be low. Glycopeptides, as a drug class, are not known to be associated with abuse potential or withdrawal phenomena, and there is no known chemical or pharmacological basis for abuse potential with dalbavancin. In addition, the potential for drug abuse is considered low due to the IV administration of dalbavancin by healthcare professionals in a hospital or clinical setting.

No TEAE representing potential abuse of dalbavancin was identified in any clinical trial performed to evaluate dalbavancin, and no epidemiologic data regarding the potential for abuse of dalbavancin exist. Additionally, there were no study drug accountability issues noted during routine monitoring of the dalbavancin clinical trial sites.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Table 36- New Safety Concerns and Reclassification With a Submission of an Updated RMP

Off Label Use	
Current classification	Not applicable as this risk has been removed from the list of safety concerns.
Previous classification	Important potential risk
Reasons for the reclassification/removal/addition to the list of safety concerns	During Xydalba's registration renewal procedure (EMEA/H/C/002840/R/0028; opinion received 19/Sep/2019), it was suggested by the EMA (Rapporteur's 2nd Updated Assessment Report) to delete the 'off-label use' from the important potential risks, as it is already well-known to health professionals and does not require additional pharmacovigilance or risk minimisation measures.

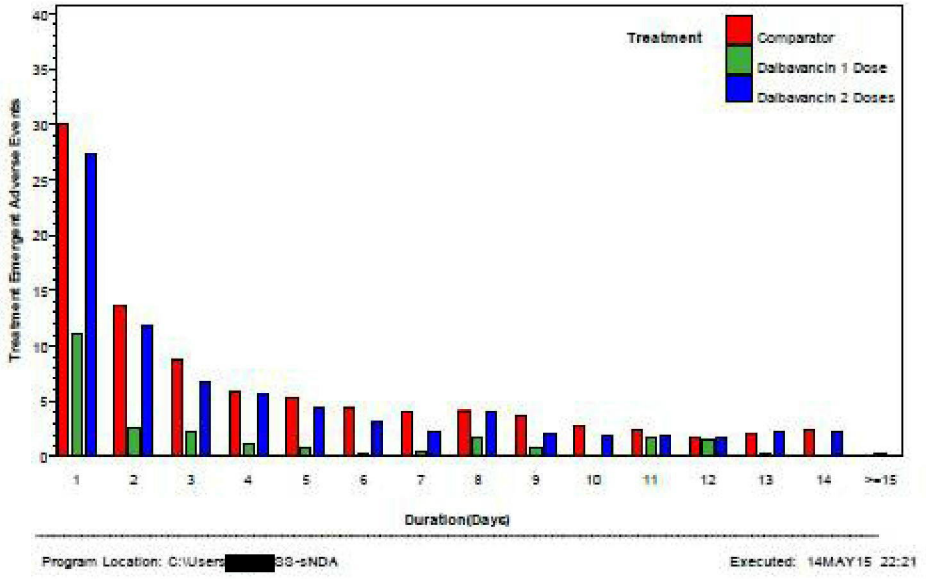
SVII.3 Details of important identified risks, important potential risks, and missing information

During the subsequent risk discussions, the data is in general provided for the Phase 2/3 overall adult safety population (see section SIII.2 Clinical Trial exposure), however in some instances additional data from the Phase 1 and Durata Phase 3 data sets are presented. The Phase 3 dataset allows for a comparison of safety data between dalbavancin and vancomycin/linezolid, the comparators used in the Phase 3 trials. Since the DLP of the Integrated Safety Summary (01 April 2015) three phase 1 studies were completed (DUR001-106, DUR001-109, and DUR001-303). No new signals have emerged from these trials. The SAEs from these studies, which are relevant for discussion of safety concerns, are commented separately in the applicable risk table. In addition, no related SAEs, SAEs pertaining to the important risks, or new signals emerged from the paediatric trials (DUR001-306, DAL-PK-02, A8841004, and DUR001-106).

A graphical display of TEAE duration is provided in Figure SVII.3-1. The mean ± SD duration of AEs was 7.5 ± 11.2 days. The median duration of AEs for patients in any regimen of dalbavancin was 3.0 days relative to 4.0 days for those in the comparator arm. In DUR001-303, the median duration of an AE was 3.0 days for both the single and two dose regimens. The percent of TEAEs with a specific duration (in days) was similar between dalbavancin-treated and comparator-treated adult subjects in the Phase 2/3 dataset and was similar between the single-dose dalbavancin group and the two-dose dalbavancin group in Study DUR001-303.

A total of 285 (11.5%) TEAEs reported in adult dalbavancin-treated subjects were ongoing at the end of the study; these events were not included in the calculation of TEAE duration.

Figure SVII.3-1 Adverse Event Duration: Phase 2/3 Adult Overall Safety Population



Source: ISS Figure 9.1

Source: Integrated CTD database: Phase 2/3 Studies (DUR001-301DUR001-302, DUR001-303, VER001-4, VER001-5, VER001-8, VER001-9, and VER001-16)

Table 37- Presentation of Important Identified and Important Potential Risks

Important Identified Risk 1: Emergence of resistance	
Characterization of Risk	**Frequency with 95 % CI** Emergence of dalbavancin resistance was not observed in clinical trials.No emergence of resistance was detected in animal infection experiments, or *in vitro* studies designed to detect development of resistance. Among more than 60,000 *S. aureus* strains tested in surveillance studies, resistance to dalbavancin was not detected. (Jones et al, 2013) Thus, the potential for emergence of resistance to dalbavancin for *S. aureus* appears to be low. At present the presence of the VanA gene cluster in another bacterium capable to provide a naïve bacterium with the resistance gene cluster necessary to induce glycopeptides resistance has not been shown. In vitro surveillance has been conducted to monitor any changes in susceptibility of key label pathogens for 5 years postapproval in the United States as part of a post-marketing requirement. The study also included isolates collected from medical centers in Europe. The objective was to identify any key pathogens that have developed resistance to dalbavancin and characterize the mechanism(s) of resistance. Yearly reports have been submitted to authorities; the fourth interim microbiological report has been submitted in the EU. As of DLP, no resistant pathogens have been identified that required follow up molecular characterization to determine mechanism(s) of resistance. **Seriousness/outcomes** Emergence of dalbavancin resistance was not observed in clinical trials. Emergence of resistance would be a serious risk, since the infections would be more difficult or even impossible to eradicate, the resistance would probably also be for the other glycopeptides, and patient should be isolated to ensure that the resistant strain is not spreading. The outcome would be increased morbidity and mortality. **Severity and nature of risk** Emergence of dalbavancin resistance was neither observed in clinical trials, nor in the exhaustive surveillance data presently accumulated. The likelihood of resistance

Important Identified Risk 1: Emergence of resistance	
	in general is higher if drug exposure does not remain above the MIC for the target organism until the burden of organisms has been significantly reduced. Dalbavancin PK allow for a single dose or once weekly dosing for 2 doses, and obviate the potential for poor compliance during that early critical time period while also providing drug exposure as high as 300 mg/L, well above the MICs for gram positive pathogens of interest. The only organisms that potentially could be selected out would be those carrying the VanA-type resistance, such as certain enterococci. VanA type resistance has not been transferable to other organisms to date. An alternative path for resistance occurs because of single step mutations, which have not been observed with glycopeptides. In vitro testing for single step mutations with dalbavancin has failed to generate resistant mutants. **Background incidence/prevalence** Searches of the published medical literature yielded no epidemiological data referencing emergence of resistance in the target population i.e., patients with ABSSSI. Only one publication was found with antimicrobial, in particular glycopeptide antibiotic, susceptibility data of SSTI isolates across the U.S. and Europe. This surveillance study, conducted in 2001, reported that 100% of isolates of *S. aureus* (MSSA and MRSA) isolated from SSTI in hospitalised patients were susceptible to vancomycin. (Jones et al, 2003) Studies with susceptibility data on all clinical isolates including SSTI, report that 99.4% to 100% of *S. aureus* (MSSA and MRSA) clinical isolates from hospitalised patients across the U.S., Europe, and the Asia-Pacific region were susceptible to vancomycin and teicoplanin. (Sader et al, 2006; Beidenbach, Bell et al, 2007) In the U.S., 100% of gram-positive *S. aureus* (oxacillin-resistant and oxacillin-susceptible) clinical isolates were susceptible to dalbavancin; 41% of these clinical isolates were from skin and soft tissue sources. (Biedenbach, Ross et al, 2007) Since 1996, vancomycin intermediate *S. aureus* (VISA) strains have been identified in Europe, Asia and the U.S., and vancomycin resistant *S. aureus* (VRSA) strains have been reported in the U.S. since 2002. (Appelbaum, 2007) Since VISA isolates also show resistance to teicoplanin, the term glycopeptide-intermediate *S. aureus* (GISA) has also been used to indicate the broader resistance profile. Epidemiological data on VISA and VRSA are sparse and interpretation is extremely limited since existing data is from case reports and antimicrobial surveillance data. The prevalence of glycopeptide hetero-resistance (hGISA) in *S. aureus* (MSSA and MRSA) clinical isolates ranges from 8% to 11%. (Rybak et al, 2007; Garnier et al, 2006) **Post-marketing experience** Cumulatively until the DLP, there have been 61 postmarketing cases which met search criteria for the important identified risk emergence of resistance. Of these 61 cases, 19 were considered serious. The case level outcomes of these serious cases were Unknown (8), Fatal (4), NA (3), Improved (1), Recovered without sequelae (2) and Recovered (1). To date, none of these cases were indicative of emergence of resistance (due to either not reporting any culture or microbiology information or dalbavancin being used for an unapproved indication in which potential resistance cannot be assessed).
Risk groups or risk factors	Hospitalised patients and persons living in institutions, such as long-term care facilities, are at risk for skin infections caused by selected bacterial pathogens resistant to antimicrobials, especially where hygiene habits (e.g. thorough hand washing, changing gowns and gloves) are insufficient. Adherence to infection control procedures is essential to the control of antimicrobial resistance spread in these settings. (WHO, 2002; Larson et al, 2007)

Important Identified Risk 1: Emergence of resistance	
Potential mechanisms	High level glycopeptide resistance, affecting both vancomycin and teicoplanin, requires the presence of the VanA gene cluster. The VanA gene cluster consists of several genes needed to substitute the altered cell wall precursor peptide D-ala-D-lac for the normal D-ala-D-ala, as well as regulatory genes that respond to both glycopeptides. Multi-genic resistance of this type cannot simply be selected by exposure to glycopeptides, but requires the presence of another organism that already possesses these determinants and can transfer them. Low level decreases in susceptibility could theoretically result from an increase in the number of glycopeptide targets in nascent peptidoglycan.
Preventability	Prudent prescribing protocols for all antibiotics have been advocated but the actual evidence that they can reduce resistance rates is mixed, and although changes to hospital regimens may reduce one resistance problem, other opportunistic bacteria may fill the vacant niche.
Potential public health impact of safety concern	There is not a perfect correlation between *in vitro* resistance and treatment failure; however, *in vitro* resistance undoubtedly increases mortality, morbidity, and cost of treatments in many settings.
Impact on the risk-benefit balance of the product	A resistant infection may be more difficult or even impossible to eradicate. Potential use of multiple consecutive or concomitant antibacterials may increase duration of treatment and incidence of adverse events. The impact would be high if resistance becomes common enough to affect the efficacy, a situation that would significantly alter the risk-benefit balance, although this has not been observed to date.
Evidence source	Module 2.5 Clinical Overview Module 5, Section 5.3.4.3.1 Summary of Microbiology Programme Scientific literature EMA Renewal

Important Identified Risk 1: Emergence of resistance	
MedDRA terms	LLTs: • Antibiotic resistant enterococcus test positive • Antibiotic resistant Staphylococcus aureus infection • Antibiotic resistant Staphylococcus test positive • Glycopeptide antibiotic resistant enterococcal infection • Glycopeptide antibiotic resistant Staphylococcus aureus infection • Infection pyogenic due to resistant bacteria PTs: • Antibiotic level below therapeutic • Antimicrobial susceptibility test resistant • Cellulitis • Drug effect decreased • Drug effect delayed • Drug effect incomplete • Drug ineffective • Drug ineffective for unapproved indication • Drug resistance • Drug tolerance • Drug tolerance increased • No therapeutic response • Pathogen resistance • Therapeutic product ineffective • Therapeutic product ineffective for unapproved indication • Therapeutic reaction time decreased • Therapeutic response decreased • Therapeutic response delayed • Treatment failure HLT Skin and subcutaneous tissue bacterial infections

Important identified Risk 2: Pseudomembranous colitis

Characterization of Risk

Frequency with 95 % CI
Cumulatively through 22 November 2015, 8 AEs pertaining to the risk of pseudomembranous colitis in 7 subjects treated with dalbavancin have been reported during Phase 2/3 clinical trials. The number (percent) of patients with reported pseudomembranous colitis (narrow SMQ) is shown by MedDRA PT in Table SVII.3-1. The number of patients was too small for confidence intervals to provide meaningful informhation.

Table SVII.3-1 Pseudomembranous colitis. Number (%) of patients with Treatment Emergent Adverse Events, ADRs, SAEs and SARs: Phase 2/3 Adult Overall Safety Population

AE Preferred Term	Total Dalbavancin (N=2842)	Total Comparator (N=1274)
Number (%) of patients with at least one AE	7 (0.2)	1 (0.1)
Number (%) of patients with at least one ADR	5 (0.2)	1 (0.1)
Number (%) of patients with at least one SAE	1	0
AE preferred terms		
Clostridium difficile colitis	5 (0.2)	1 (0.1)
Clostridium test positive	3 (0.2)	0

Overall, 7 dalbavancin patients reported 8 events versus 1 comparator patient. Five of the 7 patients (6 of the 8 events) were participants in the CRBSI study, VER001-4.

- Clostridium difficile colitis was reported in 5 (0.2%) dalbavancin-treated subjects and 1 (0.1%) comparator-treated subject. All of these events, except for 1 case of severe C. difficile colitis (dalbavancin; unrelated to study drug), were moderate and considered to be possibly related to study drug. There were some confounding factors: one patient had been on piperacillin/ tazobactam prior to randomization; a second patient had been receiving metronidazole for empiric treatment of diarrhea prior to admission; and the C. difficile colitis in a third patient was associated with severe constipation alternating with diarrhea, though the diarrhea was intermittent, mild, and considered unrelated to study drug.

- Three dalbavancin subjects also reported Clostridium test positive, including the subject above with severe C difficile colitis (dalbavancin; unrelated to study drug), a second patient at baseline (dalbavancin; unrelated to study drug), and a third where the event was considered related (dalbavancin).

Seriousness/outcomes
No patients died or experienced an SAE related to events associated with Clostridium difficile colitis, Clostridium test positive, or diarrhea. In the dalbavancin group four patients had recovered, three were recovering and one had not recovered.

Severity and nature of risk
Seven of these events were moderate in severity and one patient reported severe Clostridium difficile colitis and Clostridium test positive (not considered related to dalbavancin). This CRBSI patient had intercurrent Klebsiella bacteraemia and fever.

Important identified Risk 2: Pseudomembranous colitis	
	Background incidence/prevalence There is a wealth of data on Clostridium difficile colitis as the primary cause of nosocomial infectious diarrhoea in adult patients in the published medical literature. Antibiotics are associated with C. difficile disease in over 96% of patients who develop the disease. (Adams and Mercer, 2007) Almost all antibiotics have been associated with CDAD; the common offending antimicrobial agents include lincosamides, ß-lactams, cephalosporins, and tetracyclines. (Thielman and Wilson, 2005) The incidence of diarrhoea during antimicrobial therapy varies greatly, in part due to the class of antibiotic, length of usage and route of administration, and definition of diarrhoea along with other host factors, such as patient status (inpatient versus outpatient), age, and underlying illnesses. Epidemiological data on pseudomembranous colitis or CDAD in the context of ABSSSI was not found in the published medical literature. The epidemiology of pseudomembranous colitis, specifically CDAD, in population-based samples is available, but may not be directly generalisable to the ABSSSI patient population. In summary, across North America and Europe, the incidence of CDAD has increased significantly since the 1990's, with similar increases noted in mortality rates where C. difficile is mentioned as a potential cause of death. **Post-marketing experience** Cumulatively until the DLP, there have been 2 postmarketing cases reporting Pseudomembranous colitis. Of these 2 cases, 1 case was assessed as serious and the case level outcome was Recovered (1).
Risk groups or risk factors	In addition to the use of antimicrobials, certain host and environmental factors predispose patients to *C. difficile* colitis. Factors such as advanced age, renal insufficiency, ICU admission, severity of underlying disease, as well as setting (inpatient versus outpatient) and duration of hospitalisation play a role in developing CDAD. (Adams and Mercer, 2007; Thielman and Wilson, 2005)
Potential mechanisms	*C. difficile* produces toxins A and B, which contribute to the development of *C difficile* associated diarrhoea (CDAD). Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Dalbavancin did not have an impact on the bowel flora when tested in a phase 1 study. Of note, the treatment for *C. difficile* is oral vancomycin; the MIC of *C. difficile* for dalbavancin is 0.25 mg/L and at least 25% of dalbavancin is excreted unchanged into the gastrointestinal tract.
Preventability	Prevention of nosocomial transmission of *C. difficile* depends on careful attention to handwashing, isolation and barrier precautions, and cleaning of the physical environment throughout the duration of symptomatic disease. Strategies aimed at preventing the development of *C. difficile* diarrhoea include the prudent use of antibiotics, the use of probiotics, and passive and active immunisation. Antibiotic restriction has been shown to be associated with decreased rates of nosocomial *C. difficile* diarrhoea, and therefore programmes encouraging the proper use of antibiotics are an important preventive strategy. The use of probiotic agents throughout the duration of antibiotic use as a means of preventing *C. difficile* diarrhoea in high-risk patients has been evaluated as a possible preventive therapy, with mixed results. *C. difficile* toxin vaccines have been developed, and their safety and immunogenicity are currently being evaluated (Poutanen and Simor, 2004). The requirement for IV administration may limit use of dalbavancin to settings and indications where medical monitoring will minimise the effect of this safety concern

Important identified Risk 2: Pseudomembranous colitis	
Potential public health impact of safety concern	Pseudomembranous colitis is a well-known complication of overgrowth with *C. difficile* and is in most cases a complication of broad spectrum antibiotic therapy. Pseudomembranous colitis can also occur after treatment with almost any other antibiotic. *C. difficile*-associated disease (CDAD) causes substantial morbidity and mortality. Nosocomial re-infection with hospital-associated strains is partly responsible for recurrent CDAD. In addition, symptom-free carriers of *C difficile* are at a relatively low risk of developing CDAD, and treatment is not recommended. However, symptom-free, colonised patients may be a source for spread in hospitals.
Evidence source	Module 2.4 Non-clinical Overview; Module 2.7.4 Summary of Clinical Safety. Scientific literature
Impact on the risk-benefit balance of the product	*Clostridium difficile* infection is the most common cause of infectious health care-associated diarrhea and is a major burden to patients and the health care system. The increasing in the incidence, severity and recurrence rates of CDAD in North America and Europe present major challenges for control and management of this disease. Patients that develop CDAD during therapy with dalbavancin should discontinue the drug and receive supportive measures together with the administration of specific treatment for *Clostridium difficile.*
MedDRA terms	Narrow SMQ Pseudomembranous colitis

Important Identified Risk 3: Hypersensitivity

Characterization of Risk

Frequency with 95 % CI

Cumulatively through 22 November 2015, 143 AEs pertaining to the risk of hypersensitivity in 124 subjects treated with dalbavancin have been reported during Phase 2/3 clinical trials. The most commonly reported hypersensitivity treatment emergent adverse events – using the narrow SMQ hypersensitivity and SMQ anyphalatic reaction – is shown in Table **SVII.3-2** by MedDRA PT. Table **SVII.3-3** shows the number and percentage of patients with at least one hypersensitivity AE, ADR, SAE or SAR. Overall the percentage of patients with at least one event of hypersensitivity or anaphylactic reaction algorythm was slightly lower with dalbavancin (4.5%) than with comparator (5.1%). The most common events seen in both groups were rash (1.7% each) and urticaria (0.5 % vs 0.6%).

Table SVII.3-2 Most Commonly Reported (n>5) Hypersensitivity Treatment Emergent Adverse Events: Phase 2/3 Adult Overall Safety Population Database [Number (%) of Patients]

Preferred Term	Total Dalbavancin (N=2842)	Total Comparator (N=1274)
Rash	48 (1.7)	22 (1.7)
Urticaria	13 (0.5)	8 (0.6)
Hypersensitivity	11 (0.4)	2 (0.2)
Dyspnea	7 (0.2)	5 (0.4)
Pruritus	7 (0.2)	3 (0.2)
Dermatitis contact	6 (0.2)	8 (0.6)
Rash pruritic	6 (0.2)	3 (0.2)

Table SVII.3-3 Hypersensitivity (narrow SMQ) and Anaphylactic Reaction algorythm. Number (%) of patients with Treatment Emergent Adverse Events, ADRs, SAEs and SARs: Phase 2/3 Adult Overall Safety Population

	Total Dalbavancin (N=2842)	TotalComparator (N=1274)
Number (%) of patients with at least one AE	124 (4.4)	62 (4.9)
Number (%) of patients with at least one ADR	64 (2.3)	31 (2.4)
Number (%) of patients with at least one SAE	4 (0.1)	2 (0.2)
Number (%) of patients with at least one SAR	2 (0.1)	1 (0.1)

Important Identified Risk 3: Hypersensitivity	
	The number of patients was too small for all confidence intervals (CI) to provide meaningful information. **Seriousness/outcomes** Of the six events considered serious, 3 were considered to be true hypersensitivity events. Two in dalbavancin (urticaria and anaphylactoid reaction) and 2 in comparator (probably related face oedema; unrelated rash). The other 2 unrelated SAEs that were identified by the hypersensitivity SMQ were not considered hypersensitive reactions: One was a case of acute exacerbation of asthma in a patient with upper respiratory infection; the other SAE was a case of respiratory failure 14 days after last dose of dalbavancin in a patient with numerous adverse events of which none was indicative for hypersensivity. Of the 124 reported hypersensitivity events in the dalbavancin group, 99 events resolved, 14 events were resolving, 7 events had not resolved, and 4 events were unknown. No fatal cases have been reported. **Severity and nature of risk** The majority of events were either mild (52 %, 64/123) or moderate (39 %, 49/123) in nature, while 11 (9%) of the events were considered severe. The anaphylactoid reaction was considered to be both severe and serious. Other severe reactions which were selected by this SMQ (but not all were cases of hypersensitivity) were cardiorespiratory arrest, respiratory failure, drug eruption (each reported two times), and one case each of hypersensitivity, urticaria, generalized erythema and pruritus. All reported rashes (all types included) were mild (52/64, 81%) or moderate (12/64, 19%) no severe rashes were reported. Steven Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) are rare, life threatening, drug-induced skin reactions. The incidence of TEN is evaluated to 0.4 to 1.2 cases per million person years (Gravante et al, 2007) and of SJS from 1 to 6 cases per million years. The immunopathologic pattern of lesions suggests a cell-mediated cytotoxic reaction against epidermal cells. Antibacterial sulphonamides, anticonvulsants, oxican and pyrazolone NSAIDs, allopurinol and chlormezanone are the drugs associated with the higher risks. SJS and TEN typically begin within 4 weeks of initiating therapy, usually 7 to 21 days after the first drug exposure and sometimes a few days after the drug has been withdrawn. It occurs more rapidly with rechallenge (Roujeau J et al, 1995; Allenore-Valeyri and Roujeau, 2007). **Background incidence/prevalence** Epidemiologic data on drug hypersensitivity reactions varies widely depending on the method of data collection, validation of the outcome, and the study population. There are published reports of adverse cutaneous drug reactions (e.g., maculopapular rash, urticaria, and erythema) in hospitalised patients in association with antimicrobial agents. In these reports, the prevalence of adverse cutaneous drug reactions ranged from 0.26% to 0.36%, with antibiotics, mainly ß–lactams, as the most common offending medications. (Borch et al, 2006; Fiszenson-Albala et al, 2003) The most common types of skin reactions in these studies were exanthematous and eczematous eruptions. However, details regarding the type of infection being treated was lacking from these studies. Epidemiologic data on hypersensitivity in the context of patients with ABSSSI is limited to a few case reports of adverse cutaneous reactions (e.g., toxic epidermal necrolysis, hypersensitivity reaction/syndrome) in patients exposed to vancomycin and teicoplanin. (Craycraft et al, 2005; Lye et al, 2007)

Important Identified Risk 3: Hypersensitivity	
	Causality assessments were unclear due to exposure to multiple medications and underlying diseases in several case reports. The available epidemiologic data for hypersensitivity reactions associated with antibiotic use and glycopeptides specifically are presented in Section SI.1 under 'Main treatment options' although the data may not be directly generalisable to the ABSSSI patient. **Post-marketing experience** Cumulatively until the DLP there have been 199 postmarketing cases reporting Hypersensitivity. Of these 199 cases, 74 cases were assessed as serious. The case level outcomes of these serious cases were Recovered (37), Unknown (19), Improved (9), On-Going (4), Recovered without sequelae (3), NA (1), and Recovered with sequelae (1).
Risk groups or risk factors	Risk factors that place a person at an increased risk for an adverse cutaneous drug reaction include the offending medication, concomitant medications, underlying diseases and the severity of such conditions. (Demoly and Gomes, 2005) The prevalence of adverse cutaneous drug reactions shows that women are more affected than men, although gender differences may depend on the age group. (Demoly and Gomes, 2005)
Potential mechanisms	Hypersensitivity reactions involve immunologic sensitisation and resultant highly specific effector responses directly by lymphocytes and/or through antibodies. The specific type of reaction that may be observed with dalbavancin administration is unknown at this time.
Preventability	With regard to histamine release related syndromes, such as Red Man and the milder forms associated with flushing, following appropriate drug administration instructions regarding infusion rate is the best preventive measure. A serious anaphylactoid reaction, such as occurred in one dalbavancin patient, would occur during administration in a hospital or infusion clinic setting where early symptoms could be identified and treatment could be initiated immediately. The long half-life of dalbavancin did not appear to influence an adequate response to the emergency medication (epinephrine, hydrocortisone, midazolam, famotidine, chloropyramine, and clemastine) provided to this patient.
Potential public health impact of safety concern	No potential public health impact of hypersensitivity reactions is anticipated.
Evidence source	Module 2.4 Nonclinical Overview Module 2.5 Clinical Overview Module 2.7.4 Summary of Clinical Safety Scientific literature
Impact on the risk-benefit balance of the product	Hypersensitivity reactions with dalbavancin can range from mild to life threatening. Serious hypersensitivity reactions that can occur following dalbavancin administration should require drug discontinuation and appropriate therapy for the allergic reaction.
MedDRA terms	Narrow SMQ Hypersensitivity Narrow SMQ Anaphylactic reaction

Important Potential Risk 1: Hepatic disorders

Characterization of Risk

Frequency with 95 % CI

Cumulatively through 22 November 2015, 140 AEs pertaining to the risk of hepatic disorders in 88 subjects treated with dalbavancin have been reported during Phase 2/3 clinical trials. The most commonly reported PTs pertaining to the Narrow SMQ drug related hepatic disorders - is shown in **Table SVII.3-4** by MedDRA PT. **Table SVII.3-5** shows the number and percentage of patients with at least one drug related hepatic disorder AE, ADR, SAE or SAR. Treatment emergent adverse events were selected using the SMQ 'Drug related hepatic disorders - comprehensive search'. The number of patients was too small for confidence intervals to provide meaningful information.

The incidence of these drug related hepatic disorder events was lower in the dalbavancin (3.1 %) than in the comparator (4.0%) groups.

Table SVII.3-4 Most commonly (n>5) reported Drug related hepatic disorders Emergent Adverse Events: Phase 2/3 Adult Overall Safety Population Database [Number (%) of Patients]

Preferred Term	Total Dalbavancin (N=2842)	Total Comparator (N=1274)
Gamma-glutamyltransferase increased	38 (1.3)	26 (2.0)
Alanine aminotransferase increased	30 (1.1)	21 (1.6)
Aspartate aminotransferase increased	21 (0.7)	9 (0.7)
Liver function test abnormal	12 (0.4)	5 (0.4)
Hepatic enzyme increased	7 (0.2)	4 (0.3)
Transaminases increased	7 (0.2)	1 (0.1)

Table SVII.3-5 Drug related hepatic disorders. Number (%) of patients with Treatment Emergent Adverse Events ADRs, SAEs and SARs: Phase 2/3 Adult Overall Safety Population

	Total Dalbavancin (N=2842)	Total Comparator (N=1274)
Number (%) of patients with at least one AE	88 (3.1)	51 (4.0)
Number (%) of patients with at least one ADR	51 (1.9)	31 (2.4)
Number (%) of patients with at least one SAE	2 (0.1)	0
Number (%) of patients with at least one SAR	0	0

Seriousness/outcomes
Two dalbavancin patients (0.2%) had serious events: hepatic lesion and gastric varices for dalbavancin; and acute cholecystitis and cholecystitis for comparator. None of these events was considered related to study drug, and only the hepatic lesion did not resolve.There were no cases of Hy's law seen in the dalbavancin clinical program.
Severity and nature of risk
The majority of the treatment emergent drug related hepatic disorders experienced by patients in the Phase 2/3 studies were mild (65%, 57/88) to moderate (34%, 30/88) in severity. There was one severe AE of INR increased reported.

Hepatotoxicity was reported in 3 subjects treated with dalbavancin. They were all considered possibly related, non serious, of mild intensity and all events resolved. Two of these cases had abnormal liver function at baseline and one patient had mild elevation of liver enzymes with maximum value on day 3 and no further elevations reported upon dalbavancin rechallenge on day 8.

The proportion of patients with abnormal hepatobiliary laboratory parameters (>ULN) post baseline were similar in both treatment arms (Table **SVII.3-6**).

Table SVII.3-6 Post-baseline ALT elevations: Phase 2/3 Integrated Safety database

Parameter (post-baseline)	Dalbavancin n/N (%)	Comparator n/N (%)
Total ALT>ULN	573 /2363 (24.25%)	316 /1173 (26.94%)
ALT >ULN - 3×ULN	509 (21.5%)	282 (24%)
ALT >3 - 5×ULN	48 (2%)	24 (2%)
ALT >5 - 10×ULN	10 (0.4%)	8 (0.7%)
ALT >10xto 20xULN	4 (0.2%)	2 (0.2%)
ALT>20xULN	2 (0.08%)	0

ULN - Upper Limit of Normal

Background incidence/prevalence
Although use of antimicrobial agents is associated with numerous and varied forms of hepatotoxicity ranging from minor, asymptomatic abnormalities in liver biochemistry tests to life-threatening hepatic failure, published data on an association between glycopeptide agents and adverse hepatobiliary events were not found. Liver dysfunction is not normally regarded as an adverse event of therapy with the glycopeptide class of antibiotics; neither teicoplanin nor vancomycin cause severe liver toxicity. (Wilson, 1998)

Linezolid – also used as a comparator in several of our phase II/III studies. Althought it commonly causes elevations in liver function tests (Zyvox SmPC, 2013), it is not known to cause (serious) hepatotoxicity. Liver failure was only reported in one isolated case after prolonged use of this product (De Bus, 2010; Falagas, 2008).

Epidemiologic data on adverse hepatobiliary events in patients with ABSSSI were not found in the published medical literature. Estimates of the prevalence of elevations in aminotransferase activity range from 4% to 10% using U.S. National Health and Nutrition Examination Survey (NHANES) 1999-2002 data. (Ioannou et al, 2006) The prevalence of elevated liver enzyme levels has been reported by several researchers to be higher among males than females and higher in persons with diabetes mellitus. Many of the concomitant medications taken by patients at risk for ABSSSI are associated with abnormalities in liver enzyme levels.

Important Potential Risk 1: Hepatic disorders	
	Post-marketing experience Cumulatively until the DLP, there have been 10 postmarketing cases reporting Hepatic disorder. Of these 10 cases, 7 cases were assessed as serious. The case level outcomes of these serious cases were Unknown (2), Improved (2), Recovered (1), Fatal (1), and On-Going (1).
Risk groups or risk factors	Patients may be at risk for hepatobiliary events due to underlying illness or concomitant medications (e.g., parenteral nutrition, analgesics, lipid lowering agents) or alcohol/IV drug abuse. Severe group A streptococcal infection, including cellulitis, has been associated with liver function test abnormalities. Patients with diabetes mellitus are at increased risk of liver injury due to the high burden of non-alcoholic fatty liver disease. (Clark, 2006) Hepatobiliary AEs were reported in clinical trials more frequently in patients who had elevated baseline hepatobiliary values than those who did not. Increased risk for hepatobiliary disorder was not associated with any of the standard demographic variables (age, gender or ethnicity). No dose adjustment of dalbavancin is recommended for patients with mild hepatic insufficiency. In the absence of data to support a dosing recommendation for patients with moderate or severe hepatic insufficiency, caution should be exercised when prescribing dalbavancin to such patients.
Potential mechanisms	It is hypothesised that the presence of dalbavancin in hepatocellular membranes resulted in dose dependent alterations in membrane permeability which at lower doses and/or shorter durations were primarily manifested by leakage of intracellular enzymes into blood. The therapeutic margin decreases with increasing duration of treatment to animals, but when comparing nonclinical findings to the clinical dosing regimen there is a margin of safety. Dalbavancin is structurally similar to vancomycin and teicoplanin, glycopeptides that have a record of safe clinical use.
Preventability	There is currently no evidence that confirms dalbavancin has an adverse effect of concern on hepatic function in humans.
Potential public health impact of safety concern	As there is no evidence to confirm an effect on hepatic function in humans, the potential health effect is unknown. However, any potential health effect is conceivably reduced by the limited (single dose or 2 dose, one week apart) dosing regimen. In addition, animal studies suggest that the hepatotoxic effects are reversible with discontinuation of treatment. The requirement for IV administration may limit use of dalbavancin to settings and indications where medical monitoring will minimise the effect of this safety concern.
Evidence source	Module 2.4 Non-clinical Overview Module 2.5 Clinical Overview Module 2.7.4 Summary of Clinical Safety Scientific literature
Impact on the risk-benefit balance of the product	Most of the reported events are elevations of liver enzymes The majority of patients with acute hepatotoxicity are expected to recover completely after discontinuation of the suspect drug. Hepatotoxicity is more likely to occur in patients with previous risk factors, therefore caution should be exercised when prescribing dalbavancin to patients with moderate or severe hepatic impairment. Hepatotoxicity can lead to significant outcomes, such as acute liver failure.
MedDRA terms	Narrow SMQ Drug related hepatic disorders - comprehensive search

Important Potential Risk 2: Otovestibular toxicity

Characterization of Risk

Frequency with 95 % CI

Cumulatively through 22 November 2015, 18 AEs pertaining to the risk of otovestibular toxicity in 18 subjects treated with dalbavancin have been reported during Phase 2/3 clinical trials. The number (percent) of patients with reported ototoxicity treatment emergent adverse events is shown by MedDRA PT in Table SVII.3-7, the table also provides the number and percentage of patients with at least one otovestibular toxicity AE, ADR, SAE. The number of patients was too small for confidence intervals to provide meaningful information.

Table SVII.3-7 Otovestibular toxicity. Number (%) of patients with treatment Emergent Adverse Events, ADRs, SAEs and SARs: Phase 2/3 Adult Overall Safety Population Database

AE Preferred Term	Total Dalbavancin (N=2842)	Total Comparator (N=1274)
Number (%) of patients with at least one AE	18 (0.6)	1 (0.1)
Number (%) of patients with at least one ADR	10 (0.4%)	0
Number (%) of patients with at least one SAE	0	0
AE preferred terms:		
Hypoacusis	1 (0.0)	0
Tinnitus	5 (0.2)	1 (0.1)
Vertigo	3 (0.1)	0
Acoustic stimulation tests abnormal	2 (0.1)	0
Audiogram abnormal	2 (0.1)	0
Deafness	5 (0.2)	0

Seriousness/outcomes

None of these events was considered serious. Twelve of the dalbavancin events were recovered while the remaining 3 events were reported as recovering.

Severity and nature of risk

Most events in Phase 2/3 clinical trials in adults were reported to be mild (17/18). The remaning event of audiogram abnormal was assessed as moderate. There were no events assessed as severe in intensity.

Ototoxicity data was also collected in paediatric Study DUR001-106. Two AEs of abnormal acoustic simulation tests (one in cohort 2 y – 6 y and one in cohort 6 y - 11 y) and two AEs of abnormal audiograms (one in cohort 3 mo – 2 y and one in cohort 2 y – 6 y) were reported. All four events were non serious and assessed as not related/unlikely related to study drug. Three events were mild and one was moderate in severity. One event was confounded by cystic fibrosis and a history of chronic aminoglycoside use. One event for abnormal acoustic simulation test was recovered/resolved and the remaining events were reported with an outcome of unknown.

In general, audiology testing was difficult to perform and interpret in this subject population. Difficulties included lack of cooperation due to age and underlying illness. Despite these limitations, there was no evidence of ototoxicity in a majority

Important Potential Risk 2: Otovestibular toxicity	
	of subjects (21/34, 62%); for the remainder, no determination could be made, as 2 were lost to follow-up, 4 were uncooperative, 4 needed additional testing or had missing raw data results, 2 had distortion product otoacoustic emissions data that was difficult to interpret without additional testing, and 1 had a history confounded by chronic aminoglycoside use. Further otovestibular toxicity data was collected in the paediatric study DUR001-306. Audiologic testing has been conducted in a total of 18 children (1 in the birth to <3-months; 6 in the 2-year to <6-year cohort; 4 in the 6-year to <12-year cohort; 7 in the 12-year to 17-year cohort). Review of the audiology parameters at baseline and Day 28 in all tested subjects (overall and by age cohort) showed no evident signal of ototoxicity and test results at Day 28 remained within the clinically normal range. No bone conduction tests needed to be performed. **Background incidence/prevalence** There are reports of ototoxicity associated with vancomycin and teicoplanin use (Brummett and Fox, 1989; Bonnet et al, 2004), although there is a lack of epidemiologic data in the published medical literature to provide incidence or prevalence rates. Furthermore, the overall incidence of drug-induced ototoxicity is unknown. However, here are the incidences with a couple of selected antibiotics: Ear and labyrinth disorders (namely deafness, hearing loss, tinnitus, and vestibular disorder) are uncommon with teicoplanin. (Targocid SmPC, 2014) Tinnitus is an uncommon adverse reaction to linezolid. (Zyvox SmPC, 2013) Transient or permanent loss of hearing are uncommon, and tinnitus and dizziness are rare adverse reactions to vancomycin. (Vancomycin Actavis SmPC, 2013) Ototoxicity has been associated with serum drug levels of 80-100mg/l, but this is rarely seen when serum levels are kept at or below 30mg/l. (Vancomycin Actavis SmPC, 2013). Additionally, data referencing otovestibular toxicity, in particular tinnitus and vertigo, in patients with ABSSSI was not found in the published medical literature. The prevalence of tinnitus in the general population is estimated to range from 10% to 19% with a higher prevalence (24% to 45%) observed in older persons. (Sindhusake et al, 2003; Henry et al, 2005) Higher prevalence rates have been reported in specific patient populations, such as persons attending hearing clinics and those with occupational exposure to noise. (Sindhusake et al, 2003) Although there is an abundance of published research on ototoxicity, data interpretation is limited by the variation in outcome definition, method of data collection, and the population under study. **Post-marketing experience** Cumulatively until the DLP, there have been 2 postmarketing cases reporting Otovestibular toxicity. There were no cases that were assessed as serious.
Risk groups or risk factors	Occupational exposure to noise can be a significant hazard to one's hearing and it is often reported that the most common cause of hearing problems precipitating tinnitus is exposure to noise. Medications are frequently associated with permanent or temporary tinnitus. Age and underlying diseases or conditions, such as ear infection, allergies, head and neck trauma, are other factors associated with tinnitus. (Henry et al, 2005) Concomitant administration with ototoxic agents (such as NSAIDs, aminoglycosides, amphotericin B, diuretics, chemotherapy or narcotic analgesics) may be a risk factor. (Cianfrone, 2011) It has been postulated that vancomycin may affect the auditory system in a manner that results in augmentation of the usual ototoxicity of aminoglycoside antibiotics. (Brummett, 1993)

Important Potential Risk 2: Otovestibular toxicity	
	In Phase 2/3 integrated dalbavancin clinical studies, adverse events in patients who received concomitant administration of aminoglycosides were evaluated. No adverse events associated with ear or labyrinth disorders were reported in either dalbavancin-treated or comparator-treated patients. Renal dysfunction has been reported as a risk factor for ototoxicity (Brummett and Morrison, 1990). Complete audiology testing was performed in subjects in Phase 1 clinical studies and included 10 subjects with mild to moderate renal impairment. Results of the audiology assessment indicate no evidence of ototoxicity. In addition the risk of ototoxicity in the children under 1 year is a potential risk which will be studied in accordance with the approved PIP.
Preventability	A causal relationship between dalbavancin and otovestibular toxicity has not been established.
Impact on the risk-benefit balance of the product	All possibly related events that were reported during treatment with dalbavancin were considered mild and resolved. Otovestibular toxicity is a disabling adverse effect which can be manifested through temporary or irreversible hearing loss. The usual time of onset for drug induced otovestibular toxicity is often unpredictable, and marked hearing loss can occur even after a single dose. Additionally, hearing loss may not manifest until several weeks or months after completion of antibiotic. No therapy is currently available to reverse ototoxic damage, therefore management emphasis is on prevention
Evidence source	Scientific literature Module 2.7.4 Summary of Clinical Safety
Potential public health impact of safety concern	A causal relationship between dalbavancin and otovestibular toxicity has not been established. No likely public health impact is expected at this time.
MedDRA terms	Narrow SMQ Hearing Impairment and Narrow SMQ Vestibular disorders

Important Potential Risk 3: Nephrotoxicity

Characterization of Risk

Frequency with 95 % CI

Cumulatively through 22 November 2015, 34 AEs pertaining to the risk of nephrotoxicity in 27 subjects treated with dalbavancin have been reported during Phase 2/3 clinical trials. The number (percent) of patients with reported nephrotoxicity is shown in Table **SVII.3-8** by MedDRA PT. Table **SVII.3-9** show the number and percentage of patients with at least one neprotoxic AE, ADR, SAE or SAR. Treatment emergent adverse events were selected using the broad SMQ 'Acute renal Failure'.

The number (percent) of patients with at least one nephrotoxic treatment emergent adverse events or ADRs was lower in dalbavancin (1.0% and 0.2%) than comparator group (1.5% and 0.6%). A between-group difference of >0.2% was seen only for blood creatinine increase (0.2% dalbavancin; 0.5% comparator) and renal failure acute (0.1% dalbavancin; 0.5% comparator). The number of patients was too small for confidence intervals to provide meaningful information.

Of the 18 cases of renal failure (PTs of acute prerenal failure, renal failure, and renal failure acute), 8 occurred in dalbavancin treated subjects, and 10 in comparator-treated subjects. None of the 8 cases in dalbavancin-treated subjects were related to treatment. In comparator-treated subjects, 3 (0.2%) of the 10 cases were possibly or probably related to treatment (2 (0.2%) of the 6 events of acute renal failure were treatment-related). Systematic review of renal laboratory test parameters including BUN and serum creatinine also did not suggest nephrotoxicity in patients treated with dalbavancin

Table SVII.3-8 Nephrotoxicity (SMQ acute renal failure) Treatment Emergent Adverse Events: Phase 2/3 Adult Overall Safety Population Database [Number (%) of Patients]

Preferred Term	Total Dalbavancin (N=2842)	Total Comparator (N=1274)
Acute prerenal failure	1 (0.0)	0
Azotaemia	1 (0.0)	0
Blood creatinine increased	6 (0.2)	6 (0.5)
Blood urea increased	9 (0.3)	3 (0.2)
Nephropathy toxic	0	1 (0.1)
Protein urine present	2 (0.1)	0
Proteinuria	5 (0.2)	1 (0.1)
Renal failure	5 (0.2)	4 (0.3)
Renal failure acute	2 (0.1)	6 (0.5)
Renal function test abnormal	1 (0.0)	0
Renal impairment	0	1 (0.1)
Urine output decreased	2 (0.1)	0

Table SVII.3-9 Nephrotoxicity. Number (%) of patients with Treatment Emergent Adverse Events (broad SMQ acute renal failure), ADRs, SAEs and SARs: Phase 2/3 Adult Overall Safety Population Database

	Total Dalbavancin (N=2842)	Total Comparator (N=1274)
Number (%) of patients with at least one AE	27 (1.0)	19 (1.5)
Number (%) of patients with at least one ADR	5 (0.2)	6 (0.5)
Number (%) of patients with at least one SAE	4 (0.1)	6 (0.5)
Number (%) of patients with at least one SAR	0	3 (0.2)

Table SVII.3-11 shows the treatment emergent adverse events occurring in ≥1% of dalbavancin and comparator patients by baseline CrCl category for the five major Phase III skin studies.
Table SVII.3-12 shows renal Aes by treatment and baseline CrCl category for these studies. For both dalbavancin and comparator, the percent of patients with at least 1 renal AE generally increases as CrCl category at baseline worsens. Please note this table is based on the renal SOC class not on the SMQ used for the other tables.

Seriousness/outcomes
The events of nephrotoxicity were reported as serious in 4 dalbavancin patients, none considered related (1 renal failure; 2 renal failure acute; 1 with renal function test abnormal); and reported as serious in 6 comparator patients, 3 considered related (1 nephropathy toxic; 5 renal failure acute). None of these events had an outcome of death.The majority of the events had recovered or were recovering; in the dalbavancin group four of the events (acute prerenal failure, blood creatinine increased, renal failure acute, renal failure) had not recovered or status was unknown, compared to 5 in the comparator group.

As demonstrated in Table 34, for patients treated with dalbavancin, rates of adverse events, whether drug-related or not, were similar in the groups of patients with and without severe renal impairment. The rate of severe adverse events was slightly higher in the severe renal impairment group, but there were no treatment-related SAEs in the severe renal impairment group in the dalbavancin arm.

Severity and nature of risk
Only 6 events were considered severe, 3 for dalbavancin (1 case of azotaemia and two cases of renal failure acute and 3 for comparator.

In the DUR001-301 and DUR001-302 studies, 61/652 (9.4%) patients randomized to dalbavancin completed ≥10 days of IV placebo and 54/651 (8.3%) of patients randomized to vancomycin/linezolid received ≥10 days of IV vancomycin. These patients were evaluated for the development of nephrotoxicity (defined as a 50% increase from baseline serum creatinine or an absolute increase in serum creatinine of 0.5 mg/dL from baseline) to understand the relative effects of dalbavancin and vancomycin on renal function. This analysis demonstrated that dalbavancin-treated patients have a statistically significantly lower likelihood of developing nephrotoxicity compared to patients treated with vancomycin for 10 days (Table SVII.3-10). Notably, the total drug exposure to dalbavancin at the approved dose is 1.5 grams, relative to 28 grams for a full 14 day course of vancomycin. To the degree that total drug exposure correlates with toxicities,

<table>
<tr><td colspan="2">Important Potential Risk 3: Nephrotoxicity</td></tr>
<tr><td></td><td>the likelihood of nephrotoxicity in humans at the approved dose would be expected to be lower than vancomycin.</td></tr>
<tr><td></td><td>Table SVII.3-10 Nephrotoxicity on therapy: DUR001-301/302
<table>
<tr><th>Study Population</th><th>Dalbavancin n/N(%)</th><th>Vancomycin n/N(%)</th></tr>
<tr><td>ITT Population</td><td>21 / 637 (3.3)</td><td>31 / 638 (4.9)</td></tr>
<tr><td>DAL versus IV VAN only</td><td>21/637 (3.3)</td><td>5/54 (9.3)</td></tr>
<tr><td>Patients who received IV treatment (DAL + IV placebo or VAN) only</td><td>1 / 58 (1.7)</td><td>5 / 54 (9.3)</td></tr>
</table>
Nephrotoxicity in the DUR001-303 study was similar in both dalbavancin regimens (0.3% in the single dose treatment group and 0.9% in the two dose treatment group) and comparable to what was seen in the DUR001-301/302 studies.

Background incidence/prevalence
Epidemiological data on adverse renal effects in the context of ABSSSI is limited. One study reported that 15% of hospitalised patients with skin and soft tissue infections had acute kidney injury, defined as an increase in serum creatinine levels more than 0.5 mg/dL.

Nephrotoxicity has been reported in association with vancomycin and teicoplanin although the overall incidence of nephrotoxicity is unknown. A retrospective study of patients treated with vancomycin for suspected or proven Gram-positive infections (2005-2006) at a New York hospital found that higher doses of vancomycin (>4 grams/day) led to a greater likelihood of vancomycin-related nephrotoxicity (defined as an increase in serum creatinine of 0.5 mg/dL, or an increase of 50%, whichever was greater, on at least two consecutive days during the period from initiation of therapy to 72 hours after completion of therapy with vancomycin). (Lodise et al, 2008) No published data was found on nephrotoxicity in patients with reduced renal function. The Vancomycin Actavis SmPC adds that this risk is increased by prolonged therapy.

Available epidemiologic data of renal function, renal impairment, and acute renal failure from different population-based samples are described in Section SI.1 under ‘Main treatment options’. Prevalence data from population-based samples vary widely due to differences in the definition of the outcome and the study populations. In addition, many studies were conducted in individual hospitals for study periods less than one year.

Post-marketing experience
Cumulatively until the DLP, there have been 19 postmarketing cases reporting Nephrotoxicity. Of these 19 cases, 16 cases were assessed as serious. The case level outcomes of these serious cases were Unknown (7), Improved (3), On-Going (2), NA (1), Recovered without sequelae (1), Fatal (1), and Recovered (1).</td></tr>
<tr><td>Risk groups or risk factors</td><td>Nephrotoxicity may be associated with concurrently administered nephrotoxic drugs, such as NSAIDs, antibiotics such as aminoglycosides, beta lactams or quinolones, ACE inhibitors, diuretics, PPIs, contrast dye, or chemotherapy. The clinical information obtained on concomitant drug therapy during dalbavancin treatment does not indicate any significant drug-drug interactions, but future examinations of concomitant treatments with drugs that are nephrotoxic (and/or ototoxic) is warranted.</td></tr>
</table>

Important Potential Risk 3: Nephrotoxicity	
Potential mechanisms	Dalbavancin nephrotoxicity as observed in nonclinical toxicology studies is hypothesised to be due to the binding of dalbavancin to the anionic phospholipid components of the membranes in the renal tubular brush border, similar to what has been noted for aminoglycoside nephrotoxicity. (Kaloyanides, 1992) This binding may lead to altered membrane permeability and altered tubular function in the kidney. In an *in vitro* study using ^{14}C-dalbavancin incubated with a murine macrophage cell line (J774), most cell-associated radioactivity was membrane-associated rather than cytoplasmic, indicating a relative affinity for cellular membranes. The proposed pathogenesis of dalbavancin nephrotoxicity as observed in animal toxicology studies is essentially the same as that proposed for other cationic amphiphilic drugs that are nephrotoxic, such as aminoglycoside antibiotics. (Swan, 1997) The clinical pathology and histopathologic changes associated with dalbavancin nephrotoxicity are also very similar to those observed in toxicity studies of aminoglycosides. (Mingeot-Leclercq and Tulkens, 1999) Notably, the total drug exposure to dalbavancin at the approved dose is 1.5 grams, relative to 28 grams for a full 14 day course of vancomycin. To the degree that total drug exposure correlates with toxicities, the likelihood of nephrotoxicity in humans at the approved dose would be expected to be lower than vancomycin. The similarity of the proposed mechanism of nephrotoxicity for dalbavancin, teicoplanin and aminoglycosides might suggest the potential for additive toxicity in patients if glycopeptides and aminoglycosides are administered concurrently. Available clinical data for teicoplanin does not seem to support that there is any increased incidence of nephrotoxicity in patients receiving both classes of antibiotic concurrently. (Wilson, 1998)
Preventability	The SmPC for dalbavancin indicates dose should be reduced for patients with CrCl <30 mL/min.
Potential public health impact of safety concern	No public health impact is anticipated at this time.
Evidence source	Module 2.7.4 Summary of Clinical Safety Module 2.4 Nonclinical Overview Module 2.5 Clinical Overview Scientific literature
Impact on the risk-benefit balance of the product	Although drug induced renal impairment is often reversible if the offending drug is discontinued, the condition can be costly and may require multiple interventions, including hospitalisation. The impact is likely to be low as dalbavancin has clear instructions regarding dosing in renally impaired patients.
MedDRA terms	Broad SMQ Acute renal failure.

Table SVII.3-11 Treatment Emergent Adverse Events Occurring in ≥1% of Patients with Baseline Creatinine Clearance: Studies VER001-8 and 9; DUR001-301 and 302

	<30 mL/min		30-59 mL/min		60-89 mL/min		>=90 mL/min		Total	
Preferred Term	**Dalb. (N=29)**	**Comp. (N=21)**	**Dalb. (N=274)**	**Comp. (N=202)**	**Dalb. (N=450)**	**Comp. (N=319)**	**Dalb. (N=798)**	**Comp. (N=555)**	**Dalb. (N=1551)**	**Comp. (N=1097)**
Total number of patients with at least one AE	13 (44.8)	9 (42.9)	126 (46.0)	97 (48.0)	187 (41.6)	139 (43.6)	324 (40.6)	234 (42.2)	650 (41.9)	479 (43.7)
Alanine aminotransferase increased	0	0	4 (1.5)	3 (1.5)	1 (0.2)	5 (1.6)	11 (1.4)	10 (1.8)	16 (1.0)	18 (1.6)
Anaemia	1 (3.4)	1 (4.8)	8 (2.9)	2 (1.0)	5 (1.1)	5 (1.6)	11 (1.4)	4 (0.7)	25 (1.6)	12 (1.1)
Blood LDH increased	0	0	2 (0.7)	3 (1.5)	5 (1.1)	2 (0.6)	11 (1.4)	6 (1.1)	18 (1.2)	11 (1.0)
Cellulitis	1 (3.4)	0	6 (2.2)	4 (2.0)	3 (0.7)	7 (2.2)	10 (1.3)	6 (1.1)	20 (1.3)	17 (1.5)
Constipation	1 (3.4)	0	7 (2.6)	2 (1.0)	12 (2.7)	4 (1.3)	19 (2.4)	15 (2.7)	39 (2.5)	21 (1.9)
Diarrhoea	4 (13.8)	1 (4.8)	7 (2.6)	11 (5.4)	17 (3.8)	17 (5.3)	22 (2.8)	27 (4.9)	50 (3.2)	56 (5.1)
Dizziness	0	1 (4.8)	1 (0.4)	4 (2.0)	6 (1.3)	1 (0.3)	14 (1.8)	6 (1.1)	21 (1.4)	12 (1.1)
GGT increased	0	0	4 (1.5)	7 (3.5)	5 (1.1)	5 (1.6)	17 (2.1)	5 (0.9)	26 (1.7)	17 (1.5)
Headache	0	1 (4.8)	9 (3.3)	8 (4.0)	31 (6.9)	15 (4.7)	35 (4.4)	30 (5.4)	75 (4.8)	54 (4.9)
Hypertension	0	0	7 (2.6)	3 (1.5)	4 (0.9)	8 (2.5)	6 (0.8)	5 (0.9)	17 (1.1)	16 (1.5)
Insomnia	0	1 (4.8)	3 (1.1)	4 (2.0)	6 (1.3)	4 (1.3)	13 (1.6)	14 (2.5)	22 (1.4)	23 (2.1)
Nausea	2 (6.9)	2 (9.5)	8 (2.9)	12 (5.9)	19 (4.2)	18 (5.6)	45 (5.6)	32 (5.8)	74 (4.8)	64 (5.8)
Pruritus	0	0	5 (1.8)	3 (1.5)	9 (2.0)	8 (2.5)	13 (1.6)	15 (2.7)	27 (1.7)	26 (2.4)
Pyrexia	2 (6.9)	1 (4.8)	2 (0.7)	1 (0.5)	5 (1.1)	6 (1.9)	9 (1.1)	8 (1.4)	18 (1.2)	16 (1.5)
Rash	0	0	6 (2.2)	4 (2.0)	7 (1.6)	8 (2.5)	15 (1.9)	10 (1.8)	28 (1.8)	22 (2.0)
Urinary tract infection	1 (3.4)	0	7 (2.6)	6 (3.0)	9 (2.0)	3 (0.9)	12 (1.5)	4 (0.7)	29 (1.9)	13 (1.2)
Vomiting	3 (10.3)	2 (9.5)	9 (3.3)	5 (2.5)	10 (2.2)	5 (1.6)	20 (2.5)	14 (2.5)	42 (2.7)	26 (2.4)

Table SVII.3-12 Renal Treatment Emergent Adverse Events for Patients with Baseline Creatinine Clearance: Studies VER001-8 and 9; DUR001-301 and 302

	<30 mL/min		30-59 mL/min		60-89 mL/min		>=90 mL/min		Total	
Preferred Term	**Dalb. (N=29)**	**Comp. (N=21)**	**Dalb. (N=274)**	**Comp. (N=202)**	**Dalb. (N=450)**	**Comp. (N=319)**	**Dalb. (N=798)**	**Comp. (N=555)**	**Dalb. (N=1551)**	**Comp. (N=1097)**
Total number of patients with at least one AE	2 (6.9)	1 (4.8)	14 (5.1)	11 (5.4)	7 (1.6)	7 (2.2)	8 (1.0)	6 (1.1)	31 (2.0)	25 (2.3)
Acute prerenal failure	0	0	1 (0.4)	0	0	0	0	0	1 (0.1)	0
Azotaemia	1 (3.4)	0	0	0	0	0	0	0	1 (0.1)	0
Bladder discomfort	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)
Bladder diverticulum	0	1 (4.8)	0	0	0	0	0	0	0	1 (0.1)
Blood creatinine increased	0	0	1 (0.4)	3 (1.5)	0	2 (0.6)	0	0	1 (0.1)	5 (0.5)
Blood urea increased	0	0	4 (1.5)	2 (1.0)	2 (0.4)	1 (0.3)	0	0	6 (0.4)	3 (0.3)
Dysuria	0	0	1 (0.4)	0	2 (0.4)	0	1 (0.1)	1 (0.2)	4 (0.3)	1 (0.1)
Haematuria	0	0	2 (0.7)	1 (0.5)	1 (0.2)	0	3 (0.4)	3 (0.5)	6 (0.4)	4 (0.4)
Hydronephrosis	0	0	0	1 (0.5)	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Hypertonic bladder	0	0	1 (0.4)	0	0	0	0	0	1 (0.1)	0
Ketonuria	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0
Micturition urgency	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)
Nephrolithiasis	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0
Nephropathy toxic	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.1)
Pollakiuria	0	0	1 (0.4)	0	1 (0.2)	0	2 (0.3)	1 (0.2)	4 (0.3)	1 (0.1)
Proteinuria	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0
Pyuria	0	0	0	0	0	0	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.1)
Renal cyst	0	1 (4.8)	0	0	0	0	0	0	0	1 (0.1)
Renal disorder	0	0	0	1 (0.5)	0	0	0	0	0	1 (0.1)
Renal failure	1 (3.4)	0	2 (0.7)	2 (1.0)	0	1 (0.3)	0	0	3 (0.2)	3 (0.3)
Renal failure acute	0	0	1 (0.4)	4 (2.0)	0	1 (0.3)	0	0	1 (0.1)	5 (0.5)
Renal function test abnormal	0	0	1 (0.4)	0	0	0	0	0	1 (0.1)	0
Renal impairment	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.1)
Renal pain	0	0	0	0	0	0	2 (0.3)	0	2 (0.1)	0
Urethral stenosis	0	0	0	0	1 (0.2)	0	0	0	1 (0.1)	0

	<30 mL/min		30-59 mL/min		60-89 mL/min		>=90 mL/min		Total	
Preferred Term	**Dalb. (N=29)**	**Comp. (N=21)**	**Dalb. (N=274)**	**Comp. (N=202)**	**Dalb. (N=450)**	**Comp. (N=319)**	**Dalb. (N=798)**	**Comp. (N=555)**	**Dalb. (N=1551)**	**Comp. (N=1097)**
Urinary incontinence	0	0	0	1 (0.5)	0	0	0	0	0	1 (0.1)
Urinary retention	0	0	1 (0.4)	0	0	0	0	0	1 (0.1)	0
Urine analysis abnormal	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0

Important Potential Risk 4: Haematologic Effects

Characterization of Risk

Frequency with 95 % CI

Cumulatively through 22 November 2015, 89 Aes pertaining to the risk of haematologic effects in 64 subjects treated with dalbavancin have been reported during Phase 2/3 clinical trials. The most commonly reported haematopoietic cytopenia's is shown in Table SVII.3-13 by MedDRA PT. Table SVII.3-14 shows the number and percentage of patients with at least one drug related haematopoietic cytopenia AE, ADR, SAE or SAR. Treatment emergent adverse events were selected using the SMQ 'Haematopoietic cytopenias' and relevant sub SMQ's. The number of patients was too small for confidence intervals to provide meaningful information.

The frequency of individual adverse events was similar between subjects treated with dalbavancin and subjects treated with a comparator (0.1-1.7 %). The number of patients with at least one cytopenia was 2.3% in subjects treated with dalbavancin and 3.3% in subjects treated with comparator.

Table SVII.3-13 Most Commonly (n>2) Reported haematopoietic cytopenias Emergent Adverse Events Phase 2/3 Adult Overall Safety Population Database [Number (%) of Patients]

Preferred Term	Dalbavancin Total (N=2842)	Comparator Total (N=1274)
Anaemia	48 (1.7)	22 (1.7)
Leukopenia	9 (0.3)	7 (0.5)
Thrombocytopenia	9 (0.3)	9 (0.7)
Neutropenia	5 (0.2)	1 (0.1)
Haemoglobin decreased	4 (0.1)	0
Platelet count decreased	3 (0.1)	1 (0.1)

Table SVII.3-14 Number of patients with Emergent Adverse Events (broad SMQ haematopoietic cytopenias and sub SMQ's), ADRs, SAEs and SARs : Phase 2/3 Adult Overall Safety Population Database [Number (%) of Patients]

	Dalbavancin Total (N=2842)	Comparator Total (N=1274)
Number(%) of subjects with at least one AE	64 (2.3)	40 (3.3)
Number(%) of subjects with at least one ADR	18 (0.6)	18 (1.5)
Number(%) of subjects with at least one SAE	5 (0.2)	2(0.2)
Number(%) of subjects with at least one SAR	1 (0.0)	2 (0.2)
Number of patients with at least one AE from each SMQ		
Haematopoietic cytopenias affecting more than one type of blood cell (SMQ)	1 (0.1)	1 (0.1)
Haematopoietic erythropenia (SMQ)	46 (1.6)	21 (1.6)
Haematopoietic leukopenia (SMQ)	16 (0.6)	11 (0.9)
Haematopoietic thrombocytopenia (SMQ)	8 (0.3)	9 (0.7)
Number of patients with at least one ADR from each SMQ		
Haematopoietic cytopenias affecting more than one type of blood cell (SMQ)	0	1 (0.1)
Haematopoietic erythropenia (SMQ)	7 (0.2)	1 (0.1)
Haematopoietic leukopenia (SMQ)	9 (0.3)	7 (0.5)
Haematopoietic thrombocytopenia (SMQ)	3 (0.1)	9 (0.7)

Seriousness/outcomes

There were 5 SAE reports associated with Haematopoietic cytopenias in the phase 2/3 dataset reported on dalbavancin treatment. Only one SAE of leukopenia was assessed as probably related to dalbavancin. This was a report of a transient mild decrease of WBC which recovered without treatment, but was considered 'medically important'. The other 4 SAEs were considered unrelated to dalbavancin and thought to be related to underlying diseases: one was a case of leukopenia (attributed by the investigator to viral upper respiratory infection) 2 were cases of febrile neutropenia in patients with (very) recent history of malignancies (osteosarcoma and AML), and one was a case of anaemia in a patient with breast cancer receiving radiation therapy. All of these patients recovered. In addition to these cases of haematopoietic cytopenia's also one not related SAE of leucocytosis was reported which was considered to be a suspected atypical pneumonia in a IV drug user.

In the dalbavancin group 62% of the events recovered, and 9 events (9%) had not recovered (anaemia [n=5] and one event each of neutropenia, thrombocytopenia, Hb or Hct decreased). No fatal events had occurred.

	Severity and nature of risk Most events were mild (50/64) or moderate (22/64) and only 3 severe cases reporting the PTs of anaemia (2) and neutropenia (1), were reported. **Background incidence/prevalence** The prevalence of anaemia in population studies of healthy, nonpregnant people depends on the Haemoglobin (Hb) concentration chosen for the lower limit of normal values. The World Health Organization (WHO) chose 12.5 g/dL for both adult males and females. In the United States, limits of 13.5 g/dL for men and 12.5 g/dL for women are probably more realistic. Using these values, approximately 4% of men and 8% of women have values lower than those cited. A significantly greater prevalence is observed in patient populations. The prevalence of anaemia in Canada and northern Europe is believed to be similar to that in the United States. (Maakaron, 2013) In general, anaemia is more common in women, in particular, those in their childbearing years. In the latter decades of life, anaemia tends to occur without any particular sex predilection. Anaemia is common in patients with chronic kidney disease. (Lerma, 2014); especially those with stage III and stage IV CKD with a prevalence of 5.2% and 44.1% respectively. (CDC, 2007) A variety of drugs, such as analgesics, anaesthetics and antimicrobial agents (dapsone, rifampin, ribavirin and primaquine) have also been implicated as aetiologic factors in drug-induced anaemia, which is generally haemolytic in nature. (Coleman 1996). The incidence of drug-induced neutropenia is 1 case per million persons per year. The exact frequency of agranulocytosis is unknown; the estimated frequency is 1.0-3.4 cases per million persons per year. (Godwin, 2014) One of the most common types of thrombocytopenia in the outpatient setting is drug-induced thrombocytopenia. An epidemiologic study from Europe and the United States showed an annual incidence of 10 cases per 1 million persons, but numbers could be higher in older persons and in hospitalized patients. (van den Bemt PM, 2004) Anaemia, neutropenia and thrombocytopenia are reported uncommonly or rarely with other glycopeptide antibiotics (Targocid, 2014; Vancomycin Actavis SmPC, 2013) **Post-marketing experience** Cumulatively until the DLP, there have been 26 postmarketing cases reporting Haematologic effects. Of these 26 cases, 19 cases were assessed as serious. The case level outcomes of these serious cases were Unknown (6), On-Going (5), Recovered (4), Worsened (2), and Improved (2).

Risk groups or risk factors	Acute anaemia has a bimodal frequency distribution, affecting mostly young adults and persons in their late fifties. Causes among young adults include trauma, menstrual and ectopic bleeding, and problems of acute haemolysis. During their childbearing years, women are more likely to become iron deficient. In people aged 50-65 years, acute anaemia is usually the result of acute blood loss in addition to a chronic anemic state. This is the case in uterine and GI bleeding. Neoplasia increases in prevalence with each decade of life and can produce anaemia from bleeding, from the invasion of bone marrow with tumour, or from the development of anaemia associated with chronic disorders. Infectious aetiologies of anaemia include viral (hepatitis, infectious mononucleosis, cytomegalovirus), bacterial (Clostridia, gram-negative sepsis) and protozoal (malaria, leishmaniasis, toxoplasmosis) infections, as well as chronic infections in general. (Maakaron, 2013) Patients concurrently receiving other medications associated with leukopenia including neutropenia could be at higher risk. Numerous drugs have been associated with neutropenia, cytotoxic chemotherapy in particular. Other drugs in the highest risk categories are antithyroid medications, macrolides, and procainamides. Other antimicrobials associated with neutropenia include penicillin, cephalosporins, vancomycin, chloramphenicol, gentamicin, clindamycin, doxycycline, flucytosine, nitrofurantoin, novobiocin, minocycline, griseofulvin, lincomycin, metronidazole, rifampin, isoniazid, streptomycin, thiacetazone, mebendazole, pyrimethamine, levamisole, ristocetin, sulfonamides, chloroquine, hydroxychloroquine, quinacrine, ethambutol, dapsone, ciprofloxacin, trimethoprim, imipenem/cilastatin, zidovudine, fludarabine, acyclovir, and terbinafine. (Godwin, 2014) Medications known to cause thrombocytopenia include heparin, platelet glycoprotein (gp) Iib/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban), quinine, quinidine, sulfonamides (sulfa drugs), sulfalike drugs, chlorothiazide, chloroquine, rifampicin and gold salts. (Eke, 2014)
Preventability	There is currently no evidence that confirms dalbavancin has an adverse effect of concern on myelosuppression in humans.
Potential public health impact of safety concern	No likely public health impact is expected at this time
Evidence source	Module 2.5 Clinical Overview Scientific literature
Impact on the risk-benefit balance of the product	Although drug-induced hematologic disorders are less common than other types of adverse reactions, they are associated with significant morbidity and mortality. The primary treatment of drug induced cytopenia includes discontinuation of the suspected drug, and symptomatic measures that depend on the severity of clinical symptoms.

MedDRA terms	Broad (sub) SMQs:
	• Haematopoietic cytopenias
	  ○ Haematopoietic erythropenia
	  ○ Haematopoietic leukopenia
	Haematopoietic thrombocytopenia

Table 38- Presentation of Missing Information Topics

Missing information 1: Use in immunocompromised patients	
Evidence source(s):	These patients were excluded from the clinical development program in order to assess the safety and efficacy profile in the intended patient population without the confounder of immunosuppression. Infections in immunocompromised patients are likely to be more severe, with more associated complications and potential confounders due to concomitant chemotherapy and underlying disorders. In addition, these patients are likely to be treated in secondary or tertiary centres with higher risk of exposure to multi-drug resistant organisms.
Anticipated risk/consequence of the missing information:	Immunocompromised patients might present with infections caused by organisms that would not be pathogenic in healthy individuals, and therefore might have a different microbiological profile compared with those affecting the populations studied in clinical trials; therefore the benefit profile in this population might not be as well characterized. Population followed up for further characterization: Patients with evidence of significant immunologic disease determined by the following: an absolute neutrophil count of less than 500/mm^3, patients receiving chronic immunosuppressive drugs, and patients with known or suspected HIV with CD4 counts less than 200/uL (or with a past or current AIDS-defining condition and unknown CD4 count). Routine pharmacovigilance surveillance of lack of efficacy and off label use can be used to identify immunocompromised patients who have reduced benefits from treatment with dalbavancin.

Missing information 2: Use in patients with moderate and severe hepatic impairment	
Evidence source(s):	Patients with known bilirubin >2x the upper limit of normal were excluded in the Vicuron Phase 2/3 clinical trial program. These patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303, and pharmacokinetic studies were conducted in patients with hepatic impairment. No dose 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 (SmPC sections 4.2, 5.2).
Anticipated risk/consequence of the missing information:	The efficacy and safety has not been established in patients with moderate or severe hepatic impairment (Child-Pugh B & C). Thus, a potential consequence may be unpredictable pharmacokinetics, underdosing or overdosing. Population followed up for further characterisation: Patients with moderate and severe hepatic impairment

Missing information 3: Use in patients with a CrCl<30 ml/min receiving haemodialysis	
Evidence source(s):	Patients with known CrCl ≤50 ml/min were excluded in the Vicuron Phase 2/3 clinical trial program; these patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303, and pharmacokinetic studies were conducted in renally impaired and dialysis patients. Dose adjustment is recommended for patients with chronic renal failure if their CrCl <30 mL/min and they are not receiving regularly scheduled renal dialysis. (SmPC Sections 4.2, 5.2)
Anticipated risk/consequence of the missing information:	The efficacy and safety has not been established in this population. Thus, a potential consequence may be unpredictable pharmacokinetics, underdosing or overdosing.Population followed up for further characterisation: Patients with a CrCl<30 ml/min receiving haemodialysis

Missing information 4: Paediatric use	
Evidence source(s):	Children less than 18 years of age were not included in the adult clinical programme with the exception of two 16 year old subjects who were enrolled in VER001-4 trial. A paediatric investigation plan was agreed with the PDCO to assess ABSSSI in paediatrics prior to obtaining the marketing authorization in Europe. Ten adolescents age 12 to 16 years old were enrolled in the PK study A8841004, and 34 patients age 3 months to 11 years old were enrolled in study DUR001-106. Eight patients (neonates to infants <3 months) with suspected or confirmed bacterial infection were enrolled in PK study DAL-PK-02. A total of 198 patients with ABSSSI from birth to age <18 years old were enrolled in Study DUR001-306. Overall in Study DUR001-306, a low proportion of subjects experienced a TEAE (8.9% of subjects in dalbavancin single-dose arm, 9.0% of subjects in the dalbavancin two-dose arm, and 3.3% of subjects in the comparator arm). There were no treatment-related SAEs, no treatment-related TEAEs, no TEAEs leading to discontinuation of study intervention or study, and no SAEs leading to death in the dalbavancin single-dose or 2-dose arms. Most TEAEs were mild or moderate in severity. There was no notable difference in safety across age cohorts. Overall safety findings from the DAL-PK-02, A8841004, and DUR001-106 studies were consistent with that reported for DUR001-306. The safety and efficacy of dalbavancin for the treatment of ABSSSI has been established in paediatric patients aged from 3 months to less than 18 years. Use of dalbavancin for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data from paediatric patients. The recommended dose of dalbavancin in paediatric patients with ABSSSI with creatinine clearance of 30 ml/min/1.73m^2 and above is a single-dose regimen based on the age and weight of the paediatric patient, administered as a single infusion. The safety and efficacy of dalbavancin in children aged < 3 months old have not yet been established, therefore, no recommendation on a posology can be made.
Anticipated risk/consequence of the missing information:	Paediatric patients might be treated empirically by paediatricians. Thus, underdosing with risk of inadequate treatment of the underlying infection, or overdosing is possible. Population followed up for further characterisation: Paediatric patients

Missing information 5: Use in pregnant and lactating women	
Evidence source(s):	Dalbavancin was not studied in pregnant or lactating women. No treatment-related malformations or embryo-fetal toxicity were observed in pregnant rats or rabbits at clinically relevant exposures of dalbavancin. Treatment of pregnant rats with dalbavancin at 3.5 times the human dose on an exposure basis during early embryonic development and from implantation to the end of lactation resulted in delayed fetal maturation and increased fetal loss, respectively. Dalbavancin is not recommended during pregnancy, unless the expected benefit clearly justifies the potential risk to the foetus. Dalbavancin is excreted in the milk of lactating rats. It is not known whether dalbavancin or its metabolite is excreted in human milk; therefore, caution should be exercised when dalbavancin is administered to a nursing woman.
Population in need of further characterisation:	Babies that were breast fed while their mothers received therapy with dalbavancin. No anticipated risk or consequence is identified.
Anticipated risk/consequence of the missing information:	Possible impact on the foetus, such as developmental or congenital abnormalities. Possible impact on the pregnancy such as early miscarriage. Population followed up for further characterisation: Pregnant women treated with dalbavancin.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 39- Summary of 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
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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

In accordance with the European Legislation, an appropriate system of routine pharmacovigilance is in place to monitor drug safety and includes the following activities:

- Individual case safety report collection, evaluation, and submission to relevant authorities
    - A standard follow-up questionnaire has been developed and will be used for every serious case report. Special follow-up questionnaires have been developed for selected safety concerns (as specified below). Of note, dysglycaemia is not considered an event of special interest. Based on the available data, there is no evidence to suggest a treatment-related effect of dalbavancin on glucose homeostasis.
- Continuous surveillance of post-marketing safety data with an appropriate signal detection process that includes qualitative analyses and quantitative statistical monitoring
    - For safety concerns of nephrotoxicity and otovestibular toxicity signal detection will especially focus on risk factors (including pharmacodynamic interactions with concurrently administered drugs)
- Thorough review of aggregate adverse event information for each Periodic Safety Update Report (PSUR), with special focus on benefit/risk

Table 40- Routine Pharmacovigilance Activities

Emergence of resistance		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities including targeted follow up- questionnaire for lack of efficacy	To assure continuous monitoring of adverse events of potential resistance to dalbavancin, such as cases reported as lack of efficacy.
None	*In vitro* susceptibility surveillance studies with dalbavancin will be performed (surveillance programmes)	To monitor for the post marketing occurrence of resistance to dalbavancin, including resistance patterns and trends.

Pseudomembranous colitis		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities	To assure continuous monitoring of adverse events of potential pseudomembranous and antibiotic associated- colitis.

Hypersensitivity		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities, including a targeted follow up- questionnaire for hypersensitivity	To assure continuous monitoring of adverse events of potential hypersensitivity.

Hepatic disorders		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance, including targeted follow up- questionnaire for hepatic disorders	To assure continuous monitoring of adverse events related to hepatic disorders

Otovestibular toxicity		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities, including targeted follow up- questionnaire for otovestibular toxicity Audiologic testing for children <12 years of age in the 3 planned clinical trials in the agreed paediatric programme	To assure continuous monitoring of adverse events of potential ototoxicity especially in renal impaired patients To study whether dalbavancin can be safely used in young children.

Nephrotoxicity		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance, including a targeted follow up- questionnaire for nephrotoxicity	To assure continuous monitoring of adverse events of potential nephrotoxicity, especially in patients with reduced renal capacity

Haematologic Effects		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities including a targeted follow up questionnaire for haematopoietic -cytopenias	To assure continuous monitoring of adverse events of potential haematopoietic cytopenias

Use in immunocompromised patients		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities	To assure continuous monitoring of adverse events (including lack of efficacy) in immune-compromised patients

Use in patients with moderate and severe hepatic impairment		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities	To assure continuous monitoring of adverse events (including lack of efficacy) in patients with moderate and severe hepatic impairment

Use in patients with a CrCl<30 ml/min receiving haemodialysis		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities	To assure continuous monitoring of adverse events in patients treated with dalbavancin receiving haemodialysis

Paediatric use		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities	To monitor off label use in children and to assure continuous monitoring of adverse events reported in the paediatric population.
	Paediatric studies are ongoing in different age ranges, as per the agreed modified PIP	To conduct studies to evaluate the safety (including auditory testing) and efficacy of dalbavancin in the paediatric population.

Use in Pregnant and lactating women		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities, with targeted follow-up questionnaire for pregnancy exposure	To monitor the use of dalbavancin in pregnant and lactating women and to assure continuous monitoring of adverse events in pregnant women and offspring (including from male exposure).

All risks and relevant areas of missing information (as identified in the tables above) will be considered areas of special interest and will be monitored during ongoing signal detection processes, using MedDRA terms as described in Part II of the RMP. Targeted follow up- questionnaires are designed to gather all the necessary information for cases of emergence of resistance (lack of efficacy), hypersensitivity, hepatic disorders, otovestibular toxicity, nephrotoxicity, haematologic effects and pregnancy and lactation

exposure. These questionnaires, which are included in Part VII Annex 7B, will enable early detection of changes to the benefit-risk ratio of dalbavancin in these areas. All risks and areas of missing information will be discussed in each PSUR.

III.2 Additional Pharmacovigilance Activities

The important identified and potential risks have been well characterized during clinical studies and can be adequately managed through appropriate wording in the SmPC. If new safety data emerges in the clinical trial program or post-marketing experience that provides evidence of increase in severity, specificity, or frequency, the Pharmacovigilance/ Risk Minimisation plan will be updated accordingly and the SmPC sections will also reflect any new safety concerns.

Over the 5 year Post-Authorisation Measure surveillance period (2014 to 2018) dalbavacin has continued to demonstrate good activity against relevant organisms collected in Europe, with no notable longitudinal trends in resistance. Susceptibilty rates remain at 100% (MICs ≤0.12 µg/mL) for *S. aureus* (including MRSA), β-hemolytic streptococci (including *S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae*) and Viridans group streptococci. Vancomycin-susceptible isolates of *E. faecalis* are also 100% susceptible to dalbavancin. Additionally, all 2018 European isolates of coagulase-negative staphylococci, vancomycin-susceptible *E. faecium* and *S. pneumoniae* were inhibited by dalbavancin at concentrations ≤0.125 µg/mL.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 41- Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Table 42- Table of Completed Studies/Activities From the 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 surveillance to monitor any changes in susceptibility of key label pathogens for five years post approval in the US as part of a PMR. Study also includes isolates collected from medical centers in Europe. Category 3	To identify any key pathogens that have developed resistance to dalbavancin and characterize the mechanism(s) of resistance	Surveillance program to monitor the occurrence of resistance to dalbavancin (if any).	Completed	5-year study supplied by laboratories conducting surveillance activities. Yearly reports to be submitted to authorities and to be released in the public domain. Surveillance program results presented and published on a yearly basis in major Infectious Disease Congresses and Journals

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 43- Planned and On-Going Post-Authorisation Efficacy Studies That are Conditions of the Marketing Authorisation or That are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
None				
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION MEASURES)

V.1 Routine Risk Minimisation Measures by Safety Concern

Table 44- Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Emergence of resistance	SmPC Wording Recommendation on appropriate antibiotics use in 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." Information on the mechanism of antibiotic resistance in 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."

<table>
<tr><td>Pseudomembranous colitis</td><td>This risk is well characterised, based on clinical and post-marketing experience from other antibiotics and can be adequately managed through appropriate wording in the SmPC for dalbavancin, as described below.

<u>SmPC Wording</u>

Warning in section 4.4:
"<u>Clostridioides (formerly Clostridium) difficile-associated diarrhoea</u>
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 Clostridioides (formerly Clostridium) difficile should be considered. These patients must never be treated with medicinal products that suppress the peristalsis"

Clostridioides (formerly Clostridium) difficile colitis is listed in section 4.8 as an uncommon adverse reaction under SOC Infections and Infestations.</td></tr>
<tr><td>Hypersensitivity</td><td><u>SmPC Wording</u>

Contraindication in section 4.3:
"Hypersensitivity to the active substance or to any of the excipients listed in section 6.1"

Warning in section 4.4:
"<u>Hypersensitivity reactions</u>
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."

The following hypersensitivity reactions are listed in section 4.8:
<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></td><td>pruritus, urticaria, rash</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr>
<td>Hepatic disorder</td>
<td>
In clinical trials, hepatic function test abnormalities noted during protocol-required monitoring were reported uncommonly. None of these led to serious outcomes. Based on clinical trial data (with limited numbers of patients), routine hepatic function monitoring did not improve patient safety. The SmPC indicates that data are not available for appropriate dosing in patients with moderate or severe hepatic impairment.

SmPC Wording

Information on dosing is provided in section 4.2:
"Hepatic impairment
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 section 5.2)."

Pharmacokinetics in patients with hepatic impairment are described in 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 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."

Following liver related adverse reactions are listed in section 4.8:

<table>
<tr><th>System Organ Class</th><th>Common</th><th>Uncommon</th></tr>
<tr><td>Investigations</td><td></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, gamma-glutamyl transferase increased</td></tr>
</table>

Pertinent preclinical information is described in 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>
</tr>
</table>

Otovestibular toxicity	SmPC Wording A warning on this class adverse reaction is provided in 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 aminoglycoside, may be at increased risk."
Nephrotoxicity	SmPC Wording A warning on limited experience in patients with creatinine clearance <30 ml/min is included in 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)." Proposed wording for recommended dosage adjustments in patients with renal impairment in section 4.2: "**Renal impairment** Dose adjustments are not required for adult patients with mild or moderate renal impairment (creatinine clearance ≥ 30 to 79 ml/min). Dose adjustments are not required for adult patients receiving regularly scheduled haemodialysis (3 times/week), and dalbavancin may be administered without regard to the timing of haemodialysis. In adult patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regularly scheduled haemodialysis, the recommended dose is reduced to either 1000 mg administered as a single infusion or 750 mg followed one week later by 375 mg (see section 5.2). There is insufficient information to recommend dosage adjustment for patients younger than 18 years with creatinine clearance less than 30 ml/min/1.73m^2." This is also further elaborated in section 5.2: SmPC Wording "**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

<table>
<tr><td></td><td>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."

Pertinent preclinical information is described in 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></tr>
<tr><td>Haematologic Effects</td><td>Following haematologic effects are listed in section 4.8 tabulated list of adverse reactions:

<u>SmPC wording</u>

<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></tr>
<tr><td>Use in immunocompromised patients</td><td><u>SmPC Wording</u>
To inform healthcare providers that dalbavancin has not been studied in severely immunocompromised patients, the following wording is included in section 4.4 :
"<u>Limitations of the clinical data</u>
There is no experience with dalbavancin in the treatment of severely immunocompromised patients."</td></tr>
</table>

Use in patients with moderate and severe hepatic impairment	SmPC Wording To inform healthcare providers about available PK data available from moderate and severe hepatic impaired patients, the following wording is included in section 4.2 and 5.2 : In 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)." In 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 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 Statement in 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 dose is reduced to either 1000 mg administered as a single infusion or 750 mg followed one week later by 375 mg (see section 5.2)." Statement on limited information available in this population in 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)." Available PK data for this population is provided in 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."

Paediatric use	Current SmPC Wording Statement in 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. " EMA deferral regarding paediatric population is described in section 5.1: "**Paediatric population** The European Medicines Agency has deferred the obligation to submit results of studies with Xydalba/dalbavancin in one or more of the subsets of the paediatric population in ABSSSI (see 4.2 and 5.2 for information on paediatric use)." Available PK data for this population is provided in 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 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." Proposed SmPC Wording Statement in section 4.2: "**Paediatric population** The recommended dose of dalbavancin in paediatric patients with ABSSSI with creatinine clearance of 30 ml/min/1.73m^2 and above is a single-dose regimen based on the age and weight of the paediatric patient, administered as a single infusion. Children and adolescents aged from 6 years to less than 18 years: The recommended dose of dalbavancin in paediatric patients aged from 6 years to less than 18 years is a single dose of 18 mg/kg (maximum 1,500 mg). Infants and children aged from 3 months to less than 6 years: The recommended dose of dalbavancin in paediatric patients aged from 3 months to less than 6 years is a single dose of 22.5 mg/kg (maximum 1,500 mg)." Available PK data for this population is provided in section 5.2: "**Paediatric population** The safety and efficacy of Xydalba in children aged < 3 months old have not yet been established.

	The pharmacokinetics of dalbavancin has been evaluated in 218 individual paediatric patients [4 days to 17 years of age, including a preterm neonate (gestational age 36 weeks; n=1) and term neonates (gestational age 37 to 40 weeks; n=6)] with creatinine clearance 30 ml/min/1.73 m^2 and above. There is insufficient information to assess the exposure of Xydalba in the paediatric patients with creatinine clearance less than 30 ml/min/1.73 m^2. No clinically important differences in drug exposure between paediatric age groups (including preterm neonates) and adults are expected following administration of the age-dependent recommended single dose of Xydalba. The median plasma AUC from 0 to 120 hours (AUC_{0-120h}) of dalbavancin in paediatric patient age groups from term neonates at birth to less than 18 years is expected to be comparable to that in adult patients (AUC_{0-120h}, 10400 mg*h/L). The expected median plasma AUC_{0-120h} of dalbavancin in preterm neonates at birth (gestational age 26 weeks to <37 weeks) was approximately 60% of that in adult patients. The expected median maximum plasma concentrations (C_{max}) of dalbavancin for paediatric patient age groups ranged between approximately 53% to 70% of that in adult patients (C_{max}, 412 mg/L). However, in all paediatric age groups, the percentage of patients attaining PK/PD targets related to in vivo drug activity were 90% or higher for MICs up to 0.125 mg/L." SmPC Wording To inform healthcare providers about the lack of available data on the use of dalbavancin during pregnancy and lactation, the SmPC will recommend the following in 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 the potential expected benefit clearly justifies the potential risk to the foetus. 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." Reproductive toxicity data from preclinical studies is described in 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."
Use in pregnant and lactating women	

V.2 Additional Risk Minimisation Measures

No additional risk minimisation measures (aRMMs) are planned or proposed for dalbavancin. Routine RMMs as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1 Additional Risk Minimisation

Not applicable.

V.2.2 Removal of additional risk minimisation activities

Not applicable.

V.3 Summary table of risk minimisation measures

Table 45- Summary of Risk Minimisation Measures

Safety concern	**Routine risk minimisation activities**	**Pharmacovigilance activities**
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."	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Pseudomembranous colitis	SmPC wording Section 4.4: "*Clostridioides* (formerly ***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 *Clostridioides* (formerly *Clostridium*) *difficile* should be considered. These patients must never be treated with medicinal products that suppress the peristalsis" Section 4.8:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation activities</th><th>Pharmacovigilance activities</th></tr>
<tr><td></td><td>"SOC Infections and Infestations: Uncommon:
Clostridioides (formerly Clostridium) difficile colitis"</td><td></td></tr>
<tr><td>Hypersensitivity</td><td><u>SmPC wording</u>
Section 4.3:
"Hypersensitivity to the active substance or to any of the excipients listed in section 6.1"

Section 4.4:
"<u>Hypersensitivity reactions</u>
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:
<table>
<tr><td>System Organ Class</td><td>Common</td><td>Uncommon</td><td>Rare</td></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></td><td>pruritus, urticaria, rash</td><td></td></tr>
</table></td><td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
None

Additional pharmacovigilance activities:
None</td></tr>
<tr><td>Hepatic disorder</td><td><u>SmPC wording</u>
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."</td><td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
None

Additional pharmacovigilance activities:
None</td></tr>
</table>

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation activities</th><th>Pharmacovigilance activities</th></tr>
<tr><td></td><td>Section 4.8:

<table><tr><td>System Organ Class</td><td>Common</td><td>Uncommon</td></tr><tr><td>Investigations</td><td></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, gamma-glutamyl transferase 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></td></tr>
<tr><td>Otovestibular toxicity</td><td><u>SmPC wording</u>
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 aminoglycoside, may be at increased risk.”</td><td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
None

Additional pharmacovigilance activities:
None</td></tr>
<tr><td>Nephrotoxicity</td><td><u>SmPC wording</u>
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 adult patients with mild or moderate renal impairment (creatinine clearance ≥ 30 to 79 ml/min). Dose adjustments are not required for adult patients receiving regularly scheduled haemodialysis (3 times/week), and dalbavancin may be administered without regard to the timing of haemodialysis. In adult patients with chronic renal impairment whose creatinine clearance is < 30 ml/min and who are not receiving regularly scheduled haemodialysis, the recommended dose is reduced to either 1000 mg administered as a single infusion or 750 mg followed one week later by 375 mg (see section 5.2).

There is insufficient information to recommend dosage adjustment for patients younger than 18 years with creatinine clearance less than 30 ml/min/1.73m^2.”</td><td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
None

Additional pharmacovigilance activities:
None</td></tr>
</table>

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation activities</th><th>Pharmacovigilance activities</th></tr>
<tr><td></td><td>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 adult 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).”

SmPC Wording

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></td></tr>
<tr><td>Haematologic effects</td><td><u>SmPC wording</u>

Section 4.8 tabulated list of adverse reactions:
<table><tr><th>System Organ Class</th><th>Common</th><th>Uncommon</th></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>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
None

Additional pharmacovigilance activities:
None</td></tr>
<tr><td>Use in immunocompromised patients</td><td><u>SmPC wording</u>
Section 4.4 :
“<u>Limitations of the clinical data</u>
There is no experience with dalbavancin in the treatment of severely immunocompromised patients.”</td><td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
None

Additional pharmacovigilance activities:
None</td></tr>
</table>

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
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 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."	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with a CrCl<30 ml/min receiving haemodialysis	Proposed text in SmPC 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 dose is reduced to either 1000 mg administered as a single infusion or 750 mg followed one week later by 375 mg (see section 5.2)." SmPC Wording 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."	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Paediatric use	Current 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 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." Proposed SmPC wording Section 4.2: "**Paediatric population** The recommended dose of dalbavancin in paediatric patients with ABSSSI with creatinine clearance of 30 ml/min/1.73m^2 and above is a single-dose regimen based on the age and weight of the paediatric patient, administered as a single infusion. Children and adolescents aged from 6 years to less than 18 years: The recommended dose of dalbavancin in paediatric patients aged from 6 years to less than 18 years is a single dose of 18 mg/kg (maximum 1,500 mg). Infants and children aged from 3 months to less than 6 years: The recommended dose of dalbavancin in paediatric patients aged from 3 months to less than 6 years is a single dose of 22.5 mg/kg (maximum 1,500 mg)." Section 5.2: "**Paediatric population** The safety and efficacy of Xydalba in children aged < 3 months old have not yet been established. The pharmacokinetics of dalbavancin has been evaluated in 218 individual paediatric patients [4 days to 17 years of age, including a	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	preterm neonate (gestational age 36 weeks; n=1) and term neonates (gestational age 37 to 40 weeks; n=6)] with creatinine clearance 30 mL/min/1.73 m^2 and above. There is insufficient information to assess the exposure of Xydalba in the paediatric patients with creatinine clearance less than 30 mL/min/1.73 m^2. No clinically important differences in drug exposure between paediatric age groups (including preterm neonates) and adults are expected following administration of the age-dependent recommended single dose of Xydalba. The median plasma AUC from 0 to 120 hours (AUC_{0120h}) of dalbavancin in paediatric patient age groups from term neonates at birth to less than 18 years is expected to be comparable to that in adult patients (AUC_{0-120h}, 10400 mg*h/L). The expected median plasma AUC_{0-120h} of dalbavancin in preterm neonates at birth (gestational age 26 weeks to <37 weeks) was approximately 60% of that in adult patients. The expected median maximum plasma concentrations (C_{max}) of dalbavancin for paediatric patient age groups ranged between approximately 53% to 70% of that in adult patients (C_{max}, 412 mg/L). However, in all paediatric age groups, the percentage of patients attaining PK/PD targets related to in vivo drug activity were 90% or higher for MICs up to 0.125 mg/L."	
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 the potential expected benefit clearly justifies the potential risk to the foetus. **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."	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF THE RISK MANAGEMENT PLAN FOR XYDALBA (DALBAVANCIN)
This is a summary of the Risk Management Plan (RMP) for Xydalba. The RMP details important risks of Xydalba, how these risks can be minimised, and how more information will be obtained about Xydalba's risks and uncertainties (missing information). Xydalba's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Xydalba should be used.

This summary of the RMP for Xydalba should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xydalba's RMP.

I. The medicine and what it is used for

Current:
Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (see the SmPC for the full indication). It contains dalbavancin as the active substance and it is given by intravenous use.

Proposed:
Xydalba is indicated for the treatment of ABSSSI in adults and paediatric patients aged 3 months and older.

Further information about the evaluation of Xydalba's benefits can be found in Xydalba's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the EPAR summary landing page.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Xydalba, together with measures to minimise such risks and the proposed studies for learning more about Xydalba's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without a prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*. In addition to these measures, information about adverse reactions is collected continuously and is regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Xydalba is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Xydalba are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xydalba. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 46- Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	Emergence of resistance Pseudomembranous colitis Hypersensitivity
Important potential risks	Hepatic disorder Otovestibular toxicity Nephrotoxicity Haematologic effects
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

II.B Summary of important risks

Table 47- Summary of Important Risks

Important Identified risk: Emergence of resistance	
Evidence for linking the risk to the medicine	Module 2.5 Clinical Overview Module 5, Section 5.3.4.3.1 Summary of Microbiology Programme Scientific literature
Risk factors and risk groups	Hospitalised patients and persons living in institutions, such as long-term care facilities, are at risk for skin infections caused by selected bacterial pathogens resistant to antimicrobials, especially where hygiene habits (e.g. thorough hand washing, changing gowns and gloves) are insufficient. Adherence to infection control procedures is essential to the control of antimicrobial resistance spread in these settings. (WHO, 2002; Larson et al, 2007)
Risk minimisation measures	Routine RMMs only
Important Identified Risk: Pseudomembranous colitis	
Evidence for linking the risk to the medicine	Module 2.4 Non-clinical Overview; Module 2.7.4 Summary of Clinical Safety. Scientific literature
Risk factors and risk groups	In addition to the use of antimicrobials, certain host and environmental factors predispose patients to *C. difficile* colitis. Factors such as advanced age, renal insufficiency, ICU admission, severity of underlying disease, as well as setting (inpatient versus outpatient) and duration of hospitalisation play a role in developing CDAD. (Adams and Mercer, 2007; Thielman and Wilson, 2005)
Risk minimisation measures	Routine RMMs only

Important Identified Risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Module 2.4 Nonclinical Overview Module 2.5 Clinical Overview Module 2.7.4 Summary of Clinical Safety Scientific literature
Risk factors and risk groups	Risk factors that place a person at an increased risk for an adverse cutaneous drug reaction include the offending medication, concomitant medications, underlying diseases and the severity of such conditions. (Demoly and Gomes, 2005) The prevalence of adverse cutaneous drug reactions shows that women are more affected than men, although gender differences may depend on the age group. (Demoly and Gomes, 2005)
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Hepatic disorder	
Evidence for linking the risk to the medicine	Module 2.4 Non-clinical Overview Module 2.5 Clinical Overview Module 2.7.4 Summary of Clinical Safety Scientific literature
Risk factors and risk groups	Patients may be at risk for hepatobiliary events due to underlying illness or concomitant medications (e.g., parenteral nutrition, analgesics, lipid lowering agents) or alcohol/IV drug abuse. Severe group A streptococcal infection, including cellulitis, has been associated with liver function test abnormalities. Patients with diabetes mellitus are at increased risk of liver injury due to the high burden of non-alcoholic fatty liver disease. (Clark, 2006) Hepatobiliary AEs were reported in clinical trials more frequently in patients who had elevated baseline hepatobiliary values than those who did not. Increased risk for hepatobiliary disorder was not associated with any of the standard demographic variables (age, gender or ethnicity). No dose adjustment of dalbavancin is recommended for patients with mild hepatic insufficiency. In the absence of data to support a dosing recommendation for patients with moderate or severe hepatic insufficiency, caution should be exercised when prescribing dalbavancin to such patients.
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Otovestibular toxicity	
Evidence for linking the risk to the medicine	Scientific literature
Risk factors and risk groups	Occupational exposure to noise can be a significant hazard to one's hearing and it is often reported that the most common cause of hearing problems precipitating tinnitus is exposure to noise. Medications are frequently associated with permanent or temporary tinnitus. Age and underlying diseases or conditions, such as ear infection, allergies, head and neck trauma, are other factors associated with tinnitus. (Henry et al, 2005) Concomitant administration with ototoxic agents (such as NSAIDs, aminoglycosides, amphotericin B, diuretics, chemotherapy or narcotic analgesics) may be a risk factor. (Cianfrone, 2011) It has been postulated that vancomycin may affect the auditory system in a manner that results in augmentation of the usual ototoxicity of aminoglycoside antibiotics. (Brummett, 1993)

	In Phase 2/3 integrated dalbavancin clinical studies, adverse events in patients who received concomitant administration of aminoglycosides were evaluated. No adverse events associated with ear or labyrinth disorders were reported in either dalbavancin-treated or comparator-treated patients. Renal dysfunction has been reported as a risk factor for ototoxicity (Brummett and Morrison, 1990). Complete audiology testing was performed in subjects in Phase 1 clinical studies and included 10 subjects with mild to moderate renal impairment. Results of the audiology assessment indicate no evidence of ototoxicity. Ototoxicity data was also collected in paediatric Study DUR001-106. Two AEs of abnormal acoustic simulation tests (one in cohort 2 y – 6 y and one in cohort 6 y - 11 y) and two AEs of abnormal audiograms (one in cohort 3 mo – 2 y and one in cohort 2 y – 6 y) were reported. All four events were non serious and assessed as not related/unlikely related to study drug. Three events were mild and one was moderate in severity. One event was confounded by cystic fibrosis and a history of chronic aminoglycoside use. One event for abnormal acoustic simulation test was recovered/resolved and the remaining events were reported with an outcome of unknown. In general audiology testing was difficult to perform and interpret in this subject population. Difficulties included lack of cooperation due to age and underlying illness. Despite these limitations, there was no evidence of ototoxicity in a majority of subjects (21/34, 62%); for the remainder no determination could be made, as 2 were lost to follow-up, 4 were uncooperative, 4 needed additional testing or had missing raw data results, 2 had distortion product otoacoustic emissions data that was difficult to interpret without additional testing, and 1 had a history confounded by chronic aminoglycoside use. In addition, the risk of ototoxicity in the children under 1 year is a potential risk. Audiologic testing has been conducted in a total of 18 children in Study DUR001-306 (1 in the birth to <3-months cohort; 6 in the 2-year to < 6-year cohort; 4 in the 6-year to < 12-year cohort; 7 in the 12-year to 17-year cohort). Review of the audiology parameters at baseline and Day 28 in all tested subjects (overall and by age cohort) showed no evident signal of ototoxicity and test results at Day 28 remained within the clinically normal range. No bone conduction tests needed to be performed.
Risk minimisation measures	Routine RMMs only
Important Potential Risk: Nephrotoxicity	
Evidence for linking the risk to the medicine	Module 2.7.4 Summary of Clinical Safety Module 2.4 Nonclinical Overview Module 2.5 Clinical Overview Scientific literature
Risk factors and risk groups	Nephrotoxicity may be associated with concurrently administered nephrotoxic drugs, such as NSAIDs, antibiotics such as aminoglycosides, beta lactams or quinolones, ACE inhibitors, diuretics, PPIs, contrast dye, or chemotherapy. The clinical information obtained on concomitant drug therapy during dalbavancin treatment does not indicate any significant drug-drug interactions, but future examinations of concomitant treatments with drugs that are nephrotoxic (and/or ototoxic) is warranted.
Risk minimisation measures	Routine RMMs only

Important Potential Risk: Haematologic effects	
Evidence for linking the risk to the medicine	Module 2.5 Clinical Overview Scientific literature
Risk factors and risk groups	Acute anaemia has a bimodal frequency distribution, affecting mostly young adults and persons in their late fifties. Causes among young adults include trauma, menstrual and ectopic bleeding, and problems of acute haemolysis. During their childbearing years, women are more likely to become iron deficient. In people aged 50-65 years, acute anaemia is usually the result of acute blood loss in addition to a chronic anemic state. This is the case in uterine and GI bleeding. Neoplasia increases in prevalence with each decade of life and can produce anaemia from bleeding, from the invasion of bone marrow with tumour, or from the development of anaemia associated with chronic disorders. Infectious aetiologies of anaemia include viral (hepatitis, infectious mononucleosis, cytomegalovirus), bacterial (Clostridia, gram-negative sepsis) and protozoal (malaria, leishmaniasis, toxoplasmosis) infections, as well as chronic infections in general. (Maakaron, 2013) Patients concurrently receiving other medications associated with leukopenia including neutropenia could be at higher risk. Numerous drugs have been associated with neutropenia, cytotoxic chemotherapy in particular. Other drugs in the highest risk categories are antithyroid medications, macrolides, and procainamides. Other antimicrobials associated with neutropenia include penicillin, cephalosporins, vancomycin, chloramphenicol, gentamicin, clindamycin, doxycycline, flucytosine, nitrofurantoin, novobiocin, minocycline, griseofulvin, lincomycin, metronidazole, rifampin, isoniazid, streptomycin, thiacetazone, mebendazole, pyrimethamine, levamisole, ristocetin, sulfonamides, chloroquine, hydroxychloroquine, quinacrine, ethambutol, dapsone, ciprofloxacin, trimethoprim, imipenem/cilastatin, zidovudine, fludarabine, acyclovir, and terbinafine. (Godwin, 2014) Medications known to cause thrombocytopenia include heparin, platelet glycoprotein (gp) IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban), quinine, quinidine, sulfonamides (sulfa drugs), sulfalike drugs, chlorothiazide, chloroquine, rifampicin and gold salts. (Eke, 2014)
Risk minimisation measures	Routine RMMs only
Missing Information: Use in immunocompromised patients	
Evidence for linking the risk to the medicine	These patients were excluded from the clinical development program in order to assess the safety and efficacy profile in the intended patient population without the confounder of immunosuppression. Infections in immunocompromised patients are likely to be more severe, with more associated complications and potential confounders due to concomitant chemotherapy and underlying disorder. In addition, these patients are likely to be treated in secondary or tertiary centres with higher risk of exposure to multi-drug resistant organisms.
Anticipated risk/consequence of the missing information	Immunocompromised patients might present with infections caused by organisms that would not be pathogenic in healthy individuals, and therefore might have a different microbiological profile compared with those affecting the populations studied in clinical trials; therefore, the benefit profile in this population might not be as well characterized. Population followed up for further characterization: Patients with evidence of significant immunologic disease determined by the following: an absolute neutrophil count of less than 500/mm^3, patients receiving chronic immunosuppressive drugs, and patients with known or suspected HIV with CD4 counts less than 200/uL (or with a past or current AIDS-defininig condition and unknown CD4 count).

	Routine pharmacovigilance surveillance of lack of efficacy and off label use can be used to identify immunocompromised patients who have reduced benefits from treatment with dalbavancin.
Risk minimisation measures	Routine RMMs only
Missing Information: Use in patients with moderate and severe hepatic impairment	
Evidence for linking the risk to the medicine	Patients with known bilirubin >2x the upper limit of normal were excluded in the Vicuron Phase 2/3 clinical trial program. These patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303, and pharmacokinetic studies were conducted in patients with hepatic impairment. No dose 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 (SmPC sections 4.2, 5.2).
Anticipated risk/consequence of the missing information	The efficacy and safety has not been established in patients with moderate or severe hepatic impairment (Child-Pugh B & C). Thus, a potential consequence may be unpredictable pharmacokinetics, underdosing or overdosing. Population followed up for further characterisation: Patients with moderate and severe hepatic impairment.
Risk minimisation measures	Routine RMMs only
Missing Information: Use in patients with a CrCl<30 ml/min receiving haemodialysis	
Evidence for linking the risk to the medicine	Patients with known CrCl ≤50 ml/min were excluded in the Vicuron Phase 2/3 clinical trial program; these patients were allowed in the Durata Phase 3 studies, DUR001-301/302/303, and pharmacokinetic studies were conducted in renally impaired and dialysis patients. Dose adjustment is recommended for patients with chronic renal failure if their CrCl <30 mL/min and they are not receiving regularly scheduled renal dialysis. (SmPC Sections 4.2, 5.2).
Anticipated risk/consequence of the missing information	The efficacy and safety has not been established in this population. Thus, a potential consequence may be unpredictable pharmacokinetics, underdosing or overdosing. Population followed up for further characterisation: Patients with a CrCl<30 ml/min receiving haemodialysis
Risk minimisation measures	Routine RMMs only
Missing Information: Paediatric use	
Evidence for linking the risk to the medicine	Children less than 18 years of age were not included in the adult clinical programme with the exception of two 16 year old subjects who were enrolled in VER001-4 trial. A paediatric investigation plan was agreed with the PDCO to assess ABSSSI in paediatrics prior to obtaining the marketing authorization in Europe and the paediatric investigations are ongoing. Ten adolescents age 12 to 16 years old were enrolled in the PK study A8841004, and 34 patients age 3 months to 11 years old were enrolled in study DUR001-106. Eight patients (neonates to infants < 3 months) with suspected or confirmed bacterial infection were enrolled in PK study DAL-PK-02. A total of 198 patients with ABSSSI from birth to age < 18 years old were enrolled in Study DUR001-306. Overall in Study DUR001-306, a low proportion of subjects experienced a TEAE (8.9% of subjects in dalbavancin single-dose arm, 9.0% of subjects in the dalbavancin two-dose arm, and 3.3% of subjects in the comparator arm). There were no treatment-related SAEs, no treatment related TEAEs, no TEAEs leading to discontinuation of study intervention or study, and no SAEs leading to death in the dalbavancin single-dose or 2-dose arms. Most TEAEs were mild or moderate in severity. There was no notable difference in safety across age cohorts. Overall safety findings from the DAL-PK-02, A8841004, and DUR001-106 studies were consistent with that reported for DUR001-306.

	The safety and efficacy of dalbavancin for the treatment of ABSSSI has been established in paediatric patients aged from 3 months to less than 18 years. Use of dalbavancin for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data from paediatric patients. The recommended dose of dalbavancin in paediatric patients with ABSSSI with creatinine clearance of 30 ml/min/1.73m^2 and above is a single-dose regimen based on the age and weight of the paediatric patient, administered as a single infusion. The safety and efficacy of dalbavancin in children aged < 3 months old have not yet been established, therefore, no recommendation on a posology can be made.
Anticipated risk/consequence of the missing information	Paediatric patients might be treated empirically by paediatricians. Thus, underdosing with risk of inadequate treatment of the underlying infection, or overdosing is possible. Population followed up for further characterisation: Paediatric patients
Risk minimisation measures	Routine RMMs only
Missing Information: Use in Pregnant and Lactating Women	
Evidence for linking the risk to the medicine	Dalbavancin was not studied in pregnant or lactating women. No treatment-related malformations or embryo-fetal toxicity were observed in pregnant rats or rabbits at clinically relevant exposures of dalbavancin. Treatment of pregnant rats with dalbavancin at 3.5 times the human dose on an exposure basis during early embryonic development and from implantation to the end of lactation resulted in delayed fetal maturation and increased fetal loss, respectively. Dalbavancin is not recommended during pregnancy, unless the expected benefit clearly justifies the potential risk to the foetus. Dalbavancin is excreted in the milk of lactating rats. It is not known whether dalbavancin or its metabolite is excreted in human milk; therefore, caution should be exercised when dalbavancin is administered to a nursing woman.
Anticipated risk/consequence of the missing information	Possible impact on the foetus, such as developmental or congenital abnormalities. Possible impact on the pregnancy such as early miscarriage. Population followed up for further characterisation: Pregnant women treated with dalbavancin.
Risk minimisation measures	Routine RMMs only

II.C Post-authorisation development plan

II.C.1 Studies that are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Xydalba.

II.C.2 Other studies in the post-authorisation development plan

Table 48- Studies in post authorisation development 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 surveillance to monitor any changes in susceptibility of key label pathogens for five years post approval in the US as part of a PMR. Study also includes isolates collected from medical centers in Europe. Category 3	To identify any key pathogens that have developed resistance to dalbavancin and characterize the mechanism(s) of resistance	Surveillance program to monitor the occurrence of resistance to dalbavancin (if any).	Complete	5-year study supplied by laboratories conducting surveillance activities. Yearly reports to be submitted to authorities and to be released in the public domain. Surveillance program results presented and published on a yearly basis in major Infectious Disease Congresses and Journals.

PART VII: ANNEXES

Annex 4 - Specific Adverse Event Follow-Up Forms

The questions from these forms are used as applicable for follow-up of each serious and/or special interest adverse events.

Annex 6 - Details of proposed additional risk minimisation measures (if applicable)

Not applicable.