13 October 2022
EMA/249855/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Xydalba

International non-proprietary name: dalbavancin

Procedure No. EMEA/H/C/002840/II/0043

Note

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

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List of abbreviations

Abbreviation/Term	Definition
ABSSSI	acute bacterial skin and skin structure infection(s)
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AUC	area under the plasma concentration versus time curve
fAUC/MIC	the ratio of free drug AUC to MIC over a 24-hour period
BMI	body mass index
BSA	body surface area
C. diff	*Clostridium difficile*
CE	clinically evaluable
CL	Clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing and controls
CR-BSI	catheter-related blood stream infection
CrCl	creatinine clearance
CV	coefficient of variation
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment (visit)
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
ITT	intent-to-treat
MAA	Marketing Authorisation Application
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
MIC_{90}	minimum concentration that inhibits growth of 90% of isolates examined
microITT	microbiological ITT
mITT	modified intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
PD	Pharmacodynamic
PEC	Predicted Environmental Concentration
PI	Product information
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PL	Patient leaflet
PTA	PK/PD target attainment
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
TOC	test of cure (visit)

ULN	upper limit of normal
V	volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 29 November 2021 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to the paediatric population (aged 3 months to < 18 years) for the treatment of ABSSSI based on interim results from the safety and efficacy Phase 3 Study DUR001-306, together with data from three Phase 1 PK studies (A8841004, DUR001-106, and DAL-PK-02). Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the Summary of Product Characteristics (SmPC) were updated. The Package Leaflet (PL) has been updated accordingly.
In addition, the MAH has taken the opportunity to make minor editorial amendments and QRD updates (v10.2) to the SmPC/PL.
Version 7.0 of the RMP has also been submitted.
The MAH also requested 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0522/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0522/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Not applicable.

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	29 November 2021
Start of procedure:	26 March 2022
CHMP Rapporteur Assessment Report	20 May 2022
Updated PRAC Rapporteur Assessment Report	25 May 2022
PRAC Outcome	10 June 2022
CHMP members comments	13 June 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 June 2022
Request for supplementary information (RSI)	23 June 2022
CHMP Rapporteur Assessment Report	13 September 2022
PRAC Rapporteur Assessment Report	9 September 2022
PRAC members comments	21 September 2022
Updated PRAC Rapporteur Assessment Report	22 September 2022
PRAC Outcome	29 September 2022
CHMP members comments	03 October 2022
Updated CHMP Rapporteur Assessment Report	06 October 2022
Opinion	13 October 2022

2. Scientific discussion

2.1. Introduction

Xydalba (dalbavancin) was authorised in the EU on 19 February 2015 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. This report includes the assessment of an application for Xydalba to extend its indication to include the paediatric population (aged 3 months to < 18 years) for the treatment of acute bacterial skin and skin structure infection (ABSSSI). The proposed wording for the new therapeutic indications was (proposed amendment in ***bold italics***):

> 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.***

The application relies on the concept of extrapolation of clinical efficacy and safety based on comparable plasma exposures in children to those in adults. The acceptance of extrapolation is based on assumptions that the disease, mechanism of action and thus PK/PD are the same in paediatric patients as in adults

and therefore the doses selected should achieve similar plasma exposures and probability of PK/PD target attainment (PTA) in children as in adults.

ABSSSI is a bacterial infection of the skin and skin structures and includes major cutaneous abscesses, wound infection and cellulitis/erysipelas. The most common causative pathogens are *Staphylococcus aureus* and various types of streptococci, such as beta-haemolytic streptococci of groups A, B, C, and G. ABSSSI are among the most common infections seen in clinical practice in adults and in children. These infections may require systemic antibacterial therapy, surgical management and hospitalisation. There is a need for new antibacterial agents also for the paediatric population that will effectively treat infections caused by Gram-positive bacteria including resistant pathogens such as methicillin-resistant *S. aureus*.

2.1.1. About the product

Dalbavancin is a bactericidal lipoglycopeptide. Its mechanism of action in susceptible Gram-positive bacteria 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, thus resulting in bacterial cell death.

Dalbavancin for Injection (Xydalba), 500 mg, is a sterile, lyophilized, white to off-white to pale yellow, preservative-free solid, which must be reconstituted and diluted prior to IV administration. It was authorised in the EU on 19 February 2015 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

The recommended dose of dalbavancin in adult patients with ABSSSI is 1,500 mg administered as either a single infusion of 1,500 mg or as 1,000 mg followed one week later by 500 mg.

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 1,000 mg administered as a single infusion or 750 mg followed one week later by 375 mg.

The proposed dose in paediatric patients aged from 6 years to less than 18 years is a single dose of 18 mg/kg (maximum 1,500 mg) and in paediatric patients aged from 3 months to less than 6 years a single dose of 22.5 mg/kg (maximum 1,500 mg). No dose reduction is recommended in mild or moderate renal impairment and information available is insufficient to recommend dosage adjustment for patients younger than 18 years with creatinine clearance less than 30 ml/min/1.73 m^2.

2.1.2. The development programme

This application included updates to the safety data submitted in the original Marketing Authorisation Application (MAA), in order to support the proposed paediatric indication in patients from ≥ 3 months to < 18 years of age for ABSSSI caused by designated susceptible strains of Gram-positive microorganisms for dalbavancin (for injection). These are based on a development programme including results from the DUR001 306 study, together with data from 3 Phase 1 PK studies (A8841004, DUR001-106 and DAL PK 02), PK/PD modelling and simulations, and the data from the adult safety and efficacy studies.

2.1.3. General comments on compliance with GCP

All studies in the dalbavancin programme were and are being conducted in conformance with GCP Guidelines, ICH Guidelines E6 (1996) and E3 (1995), and CFR Title 21 Part 56, and in accordance with the ethical principles stated in the Declaration of Helsinki.

2.2. Quality aspects

The currently approved adult formulation, 500 mg powder for concentrate for solution for infusion is intended to be used also for children from 3 months of age.

The powder contains the excipients mannitol, lactose monohydrate, hydrochloric acid (pH adjustment) and sodium hydroxide (pH adjustment). After reconstitution with water for injections the vial contains 25 ml of 20 mg/ml dalbavancin. The concentrate is further diluted with 5% glucose and the diluted solution for solution must have a final concentration of 1-5 mg/ml dalbavancin. The final concentration of the excipients mannitol and lactose monohydrate will range from 0.25 mg/ml to 1.25 mg/ml.

Since the application concerns the introduction of a paediatric population, the suitability of the proposed formulation in the proposed age group was addressed, in line with the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2. No such justification has been provided but this is accepted since the proposed adult formulation only contains commonly used excipients in amounts for which no safety issues are foreseen in the proposed target age group.

A single dose of 22 mg/kg is proposed for children of 3 months to < 6 years age given a range of a final volume of 22 ml to 110 ml to be administered to children weighing 5.5 kg as a single intravenous infusion over a 30-minute period.

The proposed formulation is considered acceptable from a quality point of view. However, a dosing schedule including dilution volumes was added to the instructions in the SmPC and PL in order to minimise the risk of dosing errors and to facilitate the handling of the drug product.

2.3. Non-clinical aspects

No new non-clinical data were submitted with this application, which was considered acceptable by the CHMP.

In accordance with the Paediatric Investigation Plan (PIP) a dose range-finding study with dalbavancin in neonatal rat (00388/07GR133) and a definitive juvenile rat toxicology study of dalbavancin (LIA00402/07GR242) were performed and submitted. These studies were submitted as part of the original MAA submission regarding the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. Compliance with the PIP was confirmed.

2.3.1. Ecotoxicity/environmental risk assessment

With this application, the MAH provided an updated Environmental risk assessment (ERA) to take into account the increased patient use of the product in the juvenile population from ≥3 months age.

Phase I

Calculation of the Predicted Environmental Concentration

In the original MAA ERA submitted to support Xydalba for the treatment of ABSSSI in adults, the Predicted Environmental Concentration $PEC_{SURFACEWATER}$ was calculated to 0.00729 µg/L. This figure was based on a refined Fpen where the consumption (CONai) was 2676931500 mg/year. In the ERA initially submitted with this application, the Fpen for the paediatric population was refined using the same data.

A $PEC_{SURFACEWATER-TOTAL}$ was generated by adding the PECs for the adult and paediatric populations which resulted in a $PEC_{SURFACEWATER-TOTAL}$ of 0.02 µg/L. This is above the action limit of 0.01 µg/L where a Phase II assessment should be performed. However, no full Phase II programme has been performed and submitted. Instead, the MAH refered to a Phase II, Tier A study (OECD 209) used in the original ERA to evaluate the potential environmental impact of dalbavancin on microorganisms. The NOEC in the study was 227mg/l which gives a PNEC of 22.7 mg/l resulting in a PEC/PNEC ratio of 0.0000009. As the RQ is below 1, the MAH was of the opinion that no further studies were needed.

This conclusion was not agreed by CHMP as the calculations use for the Fpen refinement were considered to overestimate the market penetration. The MAH was therefore asked to revisit the calculations, perform new ones based on the most appropriate data.

In the response, the MAH provided a thoroughly revised ERA evaluating the potential environmental risks associated with dalbavancin use via the Xydalba product. As the unrefined $PEC_{SURFACEWATER}$ was initially calculated to 0.021 (above the Phase I action limit of 0.01 µg/L) the MAH refined the Fpen using ABSSSI prevalence data from two journals in the publication domain. According to the guidelines, the prevalence in the region with the highest prevalence of the disease should be used for calculation of the FPEN. Data provided from Germany where an FPEN (based on the published data) was found to be 0.00312, being the highest one. Use of the prevalence figure for Germany resulted in a calculated $PEC_{SURFACEWATER-REFINED}$ of 0.0064 µg/L which is below the 0.01 µg/L threshold, where a complete Phase II environmental fate and effect analysis would be expected.

Phase II

Aquatic Effect Studies

Activated Sludge, Respiration Inhibition Test (OECD 209)

The activated sludge, respiration inhibition test (ASRIT) study was completed to determine the effects of dalbavancin on activated sludge microorganisms. The microorganism respiration rate was evaluated under defined conditions in the presence of dalbavancin (test concentrations of 0.10, 1, 10, 100, and 1000 mg/L), a dilution water control, and 3,5-dichlorophenol reference toxicant. The study was completed according to OECD Guideline 209. The results were as follows:

Parameter	Time	Result (mg/L)
EC_{50}	3 Hr	> 1000
EC_{15}	3 Hr	227

Risk characterisation

A $PEC_{SURFACEWATER-TOTAL}$ of 0.00002, as calculated in Phase I, was used in this Phase II Tier A assessment.

Using the results from the dalbavancin OECD 209-study above, a PNEC was calculated following guidance from the EMA and ECHA. The EC15 was used to approximate the No-Observed-Effect Concentration (NOEC) for sludge microorganisms1 and was used to calculate the PNECMICROORGANISM.

Studied SpeciesNOEC (mg/L) - Sludge Microorganisms 227

The PNEC for the activated sludge microbial community was determined by applying an assessment factor (AF) of 10 to this value.

PNECMICROORGANISM = 227mg/L/10

PNECMICROORGANISM = 22.7 mg/L

PEC/PNECMICROORGANISM = 0.00002/22.7

PEC/PNECMICROORGANISM = 0.0000009 < Action limit of 0.1

Based on a PEC/PNECMICROORGANISM risk quotient < 0.1, dalbavancin is unlikely to represent a risk to microorganisms. No further testing is required.

Summary of Phase II Tier A Fate and Effects Analysis

Using the approach in the EMA Guideline and Q&A including the conservative assumption of no depletion due to metabolism, the PEC/PNEC ratio for dalbavancin for sludge microorganisms was calculated. The PEC/PNEC ratio for microorganisms was substantially less than 0.1. Additionally, the n-octanol-buffer distribution coefficient, Log Pow, of 2.3 does not indicate the potential for bioaccumulation in aquatic species. Therefore, based a conservative analysis of the above presented environmental data, it has been determined that dalbavancin is unlikely to represent a risk to the environment. In line with EU Directive 2001/83/EC, the European patient information leaflet includes the following general statement, for the purpose of reducing any risks to the environment with regard to the administration to patients and disposal of waste products: "*Any unused medicinal product or waste material should be disposed of in accordance with local requirements*".

2.3.2. Discussion on non-clinical aspects

No new non-clinical studies have been performed to support this change in indication. However, as part of the MAA for Xydalba in adults, a dose range-finding study and a definitive study with dalbavancin in neonatal rat (PND7-63) were submitted and assessed. The toxicity profile observed in juvenile rats was consistent with that previously observed in adult rats at the same dose levels. In repeat dose toxicology studies (up to 3 months exposure) dalbavancin was shown to induce similar systemic toxicity in both rats and dogs with kidneys, liver and the haematological system identified as the main target organs. Local and systemic toxicological changes partially reversed in parallel with decreasing plasma dalbavancin concentrations and in proportion to the length of the recovery interval. The CHMP has no objections regarding the approval of Xydalba in the paediatric population from a non-clinical perspective.

An ERA based on the ERA submitted as part of the MAA for the adult indication was submitted. A $PEC_{SURFACEWATER-TOTAL}$ was generated by adding the PECs for the adult and paediatric populations which resulted in a $PEC_{SURFACEWATER-TOTAL}$ of 0.02 µg/L. The calculations use for the Fpen refinement seemed to overestimate the market penetration and the MAH was therefore asked to revisit the calculations, perform new calculations based on the most appropriate data and justify the new calculations.

The MAH provided therefore a thoroughly revised ERA evaluating the potential environmental risks associated with dalbavancin use via the Xydalba product. The new calculated $PEC_{SURFACEWATER-REFINED}$ of 0.0064 µg/L was below the 0.01 µg/L (threshold where a complete Phase II environmental fate and effect analysis would be expected). It is therefore concluded that the ERA data for Xydalba in the proposed use have not identified a risk to the environment.

2.3.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of dalbavancin.

Considering the above data, dalbavancin is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

This extension of indication to paediatric patients (aged 3 months to <18 years) relies on the concept of extrapolation of efficacy based on comparable dalbavancin plasma exposures in children to those in adults.

GCP

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

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

- **Tabular overview of clinical studies**

Study Numbers	Age and Cohorts	Type of Study	Design
DUR001-306[a]	Cohort 1: 12 years to 17 years, inclusive Cohort 2: 6 years to < 12 years Cohort 3: 2 years to < 6 years Cohort 4: 3 months to < 2 years Cohort 5: birth to < 3 months (including preterm neonates with gestational age ≥ 32 weeks)	Phase 3, multicenter, open-label, randomized, comparator-controlled trial evaluating the safety and efficacy of a single dose of IV dalbavancin and a 2-dose regimen of once weekly IV dalbavancin (for a total of 14 days of coverage) for the treatment of ABSSSI known or suspected to be due to susceptible Gram-positive organisms in children. The comparators were either IV vancomycin (for methicillin-resistant Gram-positive infections) or IV oxacillin or flucloxacillin (for methicillin-susceptible Gram-positive infections) for 10 to 14 days.	Primary endpoint: safety. A total of 198 participants were enrolled, including 90 in the dalbavancin single-dose arm, 78 in the dalbavancin 2-dose arm, and 30 in the comparator arm.
A8841004	12 to 17 years (inclusive)	Open-label, multicenter study designed to investigate the PK, safety, and tolerability of a single dose of IV dalbavancin in 10 pediatric participants aged from 12 to 17 years of age receiving standard IV anti-infective treatment for bacterial infections.	Primary endpoints: PK parameters, safety, and tolerability. Ten subjects were assigned to study treatment: 5 subjects in the dalbavancin 1000 mg group and 5 subjects in the dalbavancin 15 mg/kg group
DUR001-106	Cohort 1: 6 to 11 years inclusive Cohort 2: 2 to < 6 years Cohort 3: 3 months to < 2 years	Phase 1, open-label, single-dose study to investigate the PK, safety, and tolerability of dalbavancin in hospitalized children aged 3 months to 11 years receiving standard IV anti-infective treatment for bacterial infections following the IV administration of a single dose of dalbavancin.	Primary endpoints: PK parameters, safety, and tolerability. 34 participants were assigned to study treatment and treated in 3 age cohorts: Cohort 1 (n = 11, 6 to 11 years of age), Cohort 2 (n = 12, 2 to < 6 years of age), and Cohort 3 (n = 11, 3 months to < 2 years of age).

Study Numbers	Age and Cohorts	Type of Study	Design
DAL-PK-02	Cohort 1: > 28 days to < 3 months Cohort 2: term neonates (gestational age ≥ 37 weeks) aged ≤ 28 days Cohort 3: preterm neonates (gestational age ≥ 32 to < 37 weeks) aged ≤ 28 days	Multicenter, randomized, open-label, single-dose study in preterm neonates to infant ages < 3 months with suspected or confirmed bacterial infection	Primary endpoints: PK parameters, safety, and tolerability. Planned number of participants: 22 Due to difficulty in recruitment, and because participants in this age range were also being enrolled in Study DUR001-306 with a similar PK sampling schedule, enrollment was stopped in October 2019. Final enrollment: 8 participants (6 in Cohort 1 and 1 each in Cohorts 2 and 3)

a To fulfil European health authority requirements for the PIP, the study will continue to enroll in Cohort 5 (birth to < 3 months) for a total of 212 participants. The study completion date is planned for December 2023 based on the latest PIP Modification.

2.4.2. Pharmacokinetics

Bioanalytical methods

The validated bioanalytical methods used in the clinical development programmes were precise and accurate, and the assay validation characteristics were acceptable. No new biopharmaceutical information/methods were provided with this submission.

popPK

Objective

This analysis was undertaken with the goal of updating a previously developed pediatric popPK model for dalbavancin, evaluate the impact of (pediatric) patient covariates on the PK of dalbavancin, and investigate target attainment for the current dosing regimen. The target attainment metrics were based on free dalbavancin exposure over MIC, in line with a previous dalbavancin target attainment analysis in adults.

The analysis represents a comprehensive popPK examination of all currently available pediatric PK data collected in three Phase I trials and one Phase III of dalbavancin in patients with ABSSSI, to support dose selection across the entire pediatric age-range.

Dataset

A total of 1124 PK observations from 211 patients were included in the model development after excluding 33 BQL observations and 18 records due to other exclusion reasons such as, pre-dose PK observations, missing PK data and outlier records based on early model fit CWRES assessment.

The three Phase 1 pediatric studies of dalbavancin for the treatment of ABSSSI have been completed. A Phase 3 pediatric comparator-controlled trial study is currently ongoing from which interim data was included in the current analysis.

Individual dalbavancin plasma concentration-time profiles on a semi-logarithmic scale, stratified by study and single or two-dose regimen were provided with data suggesting at least a biphasic disposition in the majority of the patients.

Methods

This analysis was undertaken with the goal of updating a previously developed pediatric popPK model. Because of the wide age- and weight-range of the patients included in this analysis, weight-based scaling (via allometry) of all the structural popPK parameters was considered appropriate (and necessary) from the start of model development. In addition, based on prior knowledge of dalbavancin PK in adult and pediatric populations and exploratory analysis of the current dataset, serum albumin was included as a covariate on all PK parameters and renal function (CLCRN or EGFR [for subjects younger than 2 years of age]) was included as a covariate on CL. In a subsequent stepwise covariate search, no other covariates (AGE, RACE, SEX) were found to be statistically significant.

Final popPK model

The final model was a 3-compartment model with first-order elimination, a proportional error model with a separate proportional error for the phase III study, IIV in CL, V, V2 and V3 and with estimated covariances between CL, V and V2. The final model included parameter-covariate relationships for WT (allometry) on all PK parameters (fixed allometric exponents of 0.75 for clearances and 1 for volumes), ALB on all PK parameters (the correlated effect modeled via F1) and renal function (CLCRN or EGFR) on CL. Shrinkage in ETA1(CL), ETA2(V) and ETA3 (V2) was 4%, 4% and 14% respectively.

Goodness of fit plots and visual predictive checks (VPCs)

Goodness of fit plots, pcVPS and VPCs stratified age demonstrated that the final model has good predictive performance across the full age range.

The GoF and VPCs support that the model's predictive performance is satisfactory. No major trends are seen. The pcVPC zoomed in for the first 24 h after dose support that the model is satisfactory also for early time points. The VPCs stratified on age group support that the model's predictive performance is satisfactory for all paediatric age groups including toddlers, young infants and infants. The VPCs reveal that there is less observed data in toddlers and young infants. The data is considered sufficient for the indication proposed with this application (from 3 months of age).

Simulations – methods

Using the final popPK model, dalbavancin PK was simulated for the complete pediatric age-range (pre-term neonates at birth and term neonates up to adolescents of 17.9 years of age). A simulation dataset was created for the following distinct age groups: adolescents (≥12 - < 18 y), children (≥6 - < 12 y), toddlers (≥ 2 - < 6 y), infants (≥3 months - < 2 y), young infants (≥1 month - < 3 months), term neonates (birth - < 1 month) and preterm neonates at birth (gestational age (GA) 26 weeks - < 37 weeks). The plasma concentrations were simulated for each subject at the following timepoints: 0.5 (end-of-infusion), 1 to 120, 144, and 648 h after IV dalbavancin administration. Dense sampling (hourly) up to 120h after start of treatment was applied for the calculation of AUC for the purposes of the fAUC/MIC index. For each category, sex, and regimen 500 subjects were simulated to emulate the pediatric Phase III design for a total of 7000 subjects.

Simulations – comparison of paediatric and adult exposure

Simulations of the population mean PK profiles over time for the pediatric age and adult classes, demonstrated comparable dalbavancin concentration vs. time profiles across the age-dependent dose level.

The box plots depicting the variability show a large overlap of paediatric and adult exposure, with the paediatric exposure generally slightly lower than adult reference exposure and preterm neonates appear to have the lowest AUC and Cmax.

From a safety perspective, there are no issues with the proposed paediatric posology which provide slightly lower but largely overlapping exposure as in adults.

Simulation renal impairment

Regarding paediatric patients with renal function below 30 mL/min, no data were submitted. The MAH conducted simulations using the CrCLN-CL relationship estimated for the adult population PK model. The simulations indicated that a 25-33% reduction in dose for pediatric subjects with severe renal impairment, similar to that approved for adults, is warranted. However, due to the lack of data in paediatric patients with severe renal impairment, the MAH believed that there was insufficient information to recommend a dose regimen for pediatric patients with CrCL< 30 mL/min. However, the CHMP requested a further discussion on the adequacy of the simulations in paediatric patients with CrCL< 30 mL/min/1.73m^2 and if a dose recommendation could be included for some age groups. A discussion on this issue and the final CHMP recommendations for the PI is included in section 2.4.4 (Discussion and Conclusions on clinical pharmacology).

2.4.3. PK/PD modelling

Target

Target attainment simulations were performed with the new paediatric popPK model for the revised non-clinical dalbavancin fAUC/MIC targets for stasis, 1-log kill, and 2-log kill (27.1, 53.3, and 111.1 h, respectively) (Lepak et al., 2015). The daily free dalbavancin exposure metric, (fAUCavg), used for calculating PTA, was defined as fAUC0−120/5 with the assumption of 93% of drug bound to albumin.

PTA - adults and paediatric patients

A 2-log kill target attainment for all simulated age groups with respect to MIC values ranging from 0.002 to 16 µg/mL and in relation to the MIC distributions for the 4 most relevant species of pathogens was obtained in the JMI-analyzed microbial surveillance data from 2017. The comparison between the highest observed MICs (0.25 µg/mL) and the MIC where predicted TA starts to decrease under the current treatment regimen, indicates that these regimens would continue to provide attainment of the preclinical PK/PD target for several additional MIC dilutions of pathogen potency beyond what is currently observed in the United States and Europe.

The simulated dalbavancin exposure in paediatric patients and adults were largely overlapping except for pre-term neonates. As expected, the PTA for adults and the paediatric patients, except neonates are similar. Since pre-term neonates were not included in this application, this issue was not pursued.

2.4.4. Discussion and Conclusions on clinical pharmacology

This extension of indication (to paediatric patients aged 3 months to <18 years) application relied on the concept of extrapolation of efficacy based on comparable dalbavancin plasma exposures in children to those in adults. The extrapolation approach is suitable for antibacterial agents because the PD target is expected to respond similarly to similar plasma concentrations of antibacterial agent in both adult and paediatric patients.

The popPK model used to support the proposed dosing on paediatric patients is deemed satisfactory. The exposure in paediatric patients and adult are largely overlapping, however the mean exposures lower in paediatric patients. To support that this slightly lower exposure would not risk loss of efficacy, the MAH provided PTA simulations. The simulations support the proposed paediatric dosing regimen.

From a safety perspective, there were no issues with the proposed paediatric posology as the dalbavancin

exposure in paediatric subjects results in slightly lower exposure compared to adults.

Regarding adolescents, it was unclear why above a certain body weight they cannot be dosed as adults (i.e. with a fixed dose). With the 18 mg/kg single dose and a 1500 mg maximum dose, adolescent 83 kg and above receive the same dose as adults. It may be reasonable and appropriate that adolescent above a certain body weight receive the same dose as adults. At the same time, adolescents with low body weight could be overexposed with 1500 mg flat single dose. The MAH was therefore asked to further discuss if it would be reasonable and appropriate for adolescents above a certain body weight to receive the same dose as adults. In their response the MAH indicated that the recommended dose of dalbavancin in paediatric patients aged from 6 years to 18 years is a single dose of 18 mg/kg (up to a maximum dose of 1500 mg). This corresponds to a 1500 mg single flat dose for adolescents with a body weight of 83.3 kg or above. Dalbavancin exposures using this WT-based dosing strategy resulted in simulated individual paediatric exposures that are within the range of the adult exposures observed in Phase 3. As the weight-based posology in adolescents is within the range of adult exposure from phase 3, the MAH did not propose an update of the dose to 1500 mg flat dose as adults, which was accepted by the CHMP.

Concerning the simulation on renal impairment patients, the MAH further clarified that no paediatric patients in the studies had an estimated CrCl < 30 ml/min/1.73m2 and provided simulations results for paediatric patients with renal impairment. These simulations support a dose reduction of 25-33% in paediatric patients with severe renal impairment (similar to adults).

The MAH maintained that given the lack of data in paediatric patients with severe renal impairment, there was insufficient information to recommend a dose regimen for paediatric patients in any age group with CrCl < 30 ml/min/1.73m^2. The MAH's reasoning was accepted, and the following recommendation was agreed for addition to section 4.2 of the SmPC for paediatric patients with renal impairment: "*There is insufficient information to recommend dosage adjustment for patients younger than 18 years with creatinine clearance less than 30 ml/min/1.73 m2. Currently available information is described in section 5.2, but no recommendation on a posology can be made*." Information regarding the pharmacokinetics of dalbavancin in paediatric patients was also added to section 5.2 of the SmPC. The PL was updated accordingly.

2.5. Clinical efficacy

2.5.1. Main study

DUR001-306 - A Phase 3, multicentre, open-label, randomized, comparator-controlled trial of the safety and efficacy of dalbavancin versus active comparator in paediatric subjects with acute bacterial skin and skin structure infections

Methods

Study participants

Main inclusion criteria

Cohorts 1 – 4, ages 3 months to 17 years inclusive	Cohort 5 (birth to < 3 months
Male or female patients 3 months to 17 years of age (inclusive)	Male or female patients from birth to < 3 months of age, including pre-term neonates (gestational age ≥ 32 weeks)
ABSSSI suspected or confirmed to be caused by Gram-positive bacteria, including MRSA	A clinical picture compatible with an ABSSSI suspected or confirmed to be caused by Gram-positive bacteria, including MRSA OR Suspected or confirmed sepsis including any of the following clinical criteria: a. Hypothermia (<36°C) OR fever (>38.5°C) b. Bradycardia OR tachycardia OR rhythm instability c. Hypotension OR mottled skin OR impaired peripheral perfusion d. Petechial rash e. New onset or worsening of apnoea episodes OR tachypnoea episodes OR increased oxygen requirements OR requirement for ventilation support f. Feeding intolerance OR poor sucking OR abdominal distension g. Irritability h. Lethargy04SEP2020 CSR DUR001-30641 i. Hypotonia

In addition to local signs of ABSSSI, the patient has at least one of the following: • Fever, defined as body temperature ≥ 38.4°C taken orally, ≥ 38.7°C tympanically, or ≥ 39°C rectally (core temperature) • Leucocytosis (WBC > 10,000 mm^3) or leukopenia (WBC < 2,000 mm^3) or left shift of > 10% band neutrophils	In addition, patients must meet at least one of the following laboratory criteria: a) White blood cell count ≤4.0 × 109/L OR ≥20.0 × 109/L b) Immature to total neutrophil ratio >0.2 c) Platelet count ≤100 × 109/L d) C-reactive protein (CRP) >15 mg/L OR procalcitonin ≥ 2 ng/mL e) Hyperglycaemia OR Hypoglycaemia f) Metabolic acidosis
	Infections must be of sufficient severity to merit hospitalization and parenteral antibiotic therapy.

Main exclusion criteria

- Patients in Cohort 1-4: Clinically significant renal impairment, defined as creatinine clearance < 30 mL/min (calculated by the Schwartz "bedside" formula). Patients in Cohort 5 (birth to < 3 months of age): Moderate or severe renal impairment defined as serum creatinine ≥ 2 times the upper limit of normal (× ULN) for age OR urine output < 0.5 mL/kg/h (measured over at least 8 hours prior to dosing) OR requirement for dialysis.
- Clinically significant hepatic impairment, defined as serum bilirubin or alkaline phosphatase > 2X ULN for age, and/or serum AST or ALT > 3X ULN for age.
- Patients with sustained shock defined as systolic blood pressure < 90 mm Hg in children ≥ 10 years old, < 70 mm Hg + [2 x age in years] in children 1 to < 10 years, or < 70 mm Hg in infants 3 to < 12 months old for more than 2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion or need for sympathomimetic agents to maintain blood pressure
- More than 24 hours of any systemic antibacterial therapy within 96 hours before randomization. EXCEPTION: Microbiological or clinical treatment failure with a systemic antibiotic other than IV study drug that was administered for at least 48 hours. Failure must be confirmed by either a microbiological laboratory report or documented worsening clinical signs or symptoms
- Infection due to an organism known prior to study entry to be resistant to dalbavancin (dalbavancin MIC > 0.25 µg/mL) or vancomycin (vancomycin MIC > 2 µg/mL)

Treatments

Dalbavancin: single dose IV infused over 30 minutes

- Age ≥ 3 months to < 6 years: 22.5 mg/kg on Day 1 (maximum 1500 mg)
- Age ≥ 6 years to 17 years old (inclusive): 18 mg/kg on Day 1 (maximum 1500 mg)

Dalbavancin: 2 IV doses infused over 30 minutes 1 week apart

- Age ≥ 3 months to < 6 years: 15 mg/kg on Day 1, 7.5 mg/kg on Day 8 (maximum 1000 mg Day 1; maximum 500 mg on Day 8)

- Age ≥ 6 years to 17 years old (inclusive): 12 mg/kg on Day 1, 6 mg/kg on Day 8 (maximum 1000 mg Day 1; maximum 500 mg on Day 8)

All participants in the youngest age cohort (Cohort 5: birth to < 3 months of age) received the single-dose regimen of dalbavancin (22.5 mg/kg)

Comparator: a 10 to 14-day course of IV vancomycin (for methicillin-resistant Gram-positive infections) or IV oxacillin or flucloxacillin (for methicillin-susceptible Gram-positive infections based on local practice patterns and approvals for clinical use in the paediatric population)

- Vancomycin 10 to 15 mg/kg/dose, infused over 60 (±10) minutes every 6 (±1) hours (maximum 4000 mg/day)
- Oxacillin 30 mg/kg/dose, infused over 60 (±10) minutes every 6 (±1) hours
- Flucloxacillin 50 mg/kg/dose, infused over 60 (±10) minutes every 6 (±1) hours (maximum 2000 mg/day)

Participants could be switched from IV oxacillin or flucloxacillin to oral cefadroxil (dose for infants and children:

15 mg/kg/dose every 12 hours, maximum 2 g/day; dose for adolescents: 500-1000 mg every 12 hours) after at least 72 hours of study drug treatment, if they met specified criteria for oral therapy.

Participants could be switched from IV vancomycin to oral clindamycin (10 mg/kg every 8 hours) after at least 72 hours of parenteral antibiotic therapy, if they met specified criteria for oral therapy.

Objectives and endpoints

The primary purpose of this study was to determine the safety and descriptive efficacy of dalbavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in children, from birth to 17 years (inclusive), known or suspected to be caused by susceptible Gram-positive organisms, including methicillin-resistant strains of *S. aureus*.

Objectives	Endpoints
Primary	
• To determine the safety of dalbavancin for the treatment of ABSSSI infections in children, from birth to 17 years (inclusive), known or suspected to be caused by susceptible Gram-positive organisms, including methicillin-resistant strains of *Staphylococcus aureus*	• The primary outcome measure was the safety of dalbavancin for the treatment of ABSSSI in children including the following: ○ Physical examination, vital signs, adverse events, deaths (Cohort 5 only), and clinical laboratory tests ○ Audiologic testing in at least 20 children < 12 years old performed at Baseline and repeated at Day 28 (± 2 days) ○ Impact of dalbavancin on bowel flora evaluated in all participants from birth to < 2 years by performing polymerase chain reaction (PCR) for *Clostridium difficile* (*C diff*) and culture for vancomycin-resistant enterococci (VRE) on a stool specimen or rectal swab

Objectives	Endpoints
Secondary	
• To assess clinical response at 48-72 hours post randomization in participants who did not receive rescue therapy and were alive; and clinical response based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy); at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy).	Clinical response, in each of the 5 cohorts, was assessed in participants who did not receive rescue therapy and were alive. • Clinical response at 48-72 hours after randomization was defined as ○ Cohorts 1-4: ≥ 20% reduction in lesion size compared to baseline ○ Cohort 5 participants with ABSSSI: cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions ○ Cohort 5 participants with sepsis: improvement of at least one abnormal clinical and laboratory parameter related to sepsis • Clinical response at remaining time-points based primarily on the global clinical assessment of the participant made by the investigator at that evaluation time-point. ○ Clinical response at end of treatment (EOT) visit (14 ± 2 days) defined as Cure, Improvement, Failure, or Unknown ○ Clinical response at the test of cure (TOC) visit (28 ± 2 days) and at the follow-up visit (54 ± 7 days) defined as Cure, Failure or Unknown
• To assess clinical response by baseline pathogen at 48-72 hours post randomization; and clinical response based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy).	• Clinical response was determined by baseline pathogen at 48-72 hours post randomization, EOT, TOC, and last follow-up visit, as described above. Direct demonstration of eradication or persistence of the causative organism had to be attempted in all participants where it was considered standard practice. However, this had to be done in all participants who were considered treatment failures.
• Cohort 5 (birth to < 3 months): to assess all-cause mortality at test of cure visit (28 ± 2 days after start of therapy)	• Cohort 5 only (birth to < 3 months): all-cause mortality was determined at test of cure visit (28 ± 2 days after start of therapy)
• To evaluate the pharmacokinetics (PK) of dalbavancin in pediatric participants from birth to 17 years of age (inclusive).	• Concentration of dalbavancin in plasma. • The population PK profile of dalbavancin was assessed using a sparse sampling approach and will be reported separately.

Sample size

Planned: approximately 188 participants, with 178 participants 3 months or older randomized to receive dalbavancin (single-dose or 2-dose regimen) or comparator.

The study was primarily a PK and safety study. The sample size was not based on a power calculation for hypothesis testing.

Randomisation

There was a 3:3:1 randomization scheme: 76 participants were to be randomized to dalbavancin (single dose IV), 76 to dalbavancin (2 doses once weekly IV therapy), and 26 to comparator (IV vancomycin or IV oxacillin or flucloxacillin). The randomization scheme did not include the youngest age cohort (birth to < 3 months of age), as all 10 participants in this cohort were to receive the single-dose regimen of dalbavancin, bringing the total number of participants planned to be enrolled in the study to approximately 188.

Blinding (masking)

The study was open label.

Statistical methods

Analysis Populations

- Intent-to-Treat (ITT): All randomized participants regardless of whether or not they received study drug.
- Safety: All participants in the ITT population who received at least 1 dose of study drug.
- Modified Intent-to-Treat (mITT): All randomized participants who received at least 1 dose of study drug and had a diagnosis of ABSSSI (or a suspected or confirmed sepsis for Cohort 5) not known to be caused exclusively by a Gram-negative organism.
- Clinically Evaluable (CE): Four CE populations were defined based on the timing of the outcome assessment, CE-48-72 hours (post randomization), CE-EOT, CE-TOC, and CE-Follow-up visit.
- Microbiological ITT (microITT): All participants in the ITT population who had at least 1 Gram-positive pathogen isolated at baseline.
- Microbiologically Evaluable (ME): Participants who met all of the criteria for the CE population and microITT population. Four ME populations were defined based on the timing of the outcome assessment, ME-48-72 hours (post randomization), ME-EOT, ME-TOC, and ME-Follow-up visit.

Efficacy

Efficacy analyses were based on the mITT Population and specified CE, microITT, and ME populations. No statistical testing was planned for the efficacy endpoints.

Safety

Safety analyses were based on the safety population. Participants who received the wrong regimen of study drug for their entire course of treatment were analysed in the group based on the regimen received.

Results

Participant flow

A total of 204 subjects were screened of which 6 were screen failures. Overall, 198 participants were enrolled.

Recruitment

Study Centres: United States (6), Guatemala (2), Mexico (1), Panama (1), Bulgaria (8), Georgia (4), Ukraine (2), Latvia (1), Greece (2), Spain (1), South Africa (2).

Conduct of the study

Prior to database lock, there were 6 amendments to the original protocol.

There were no changes to planned analysis methods from what was described in the protocol and detailed in the SAP.

A total of 70 participants (35.4%) had significant protocol deviations: study procedure (47 participants, 23.7%); informed consent (8 participants, 4.0%); inclusion criteria (8 participants, 4.0%); study intervention dosing non-compliance (7 participants, 3.5%); exclusion criteria (7 participants, 3.5%); and wrong study intervention dose (5 participants, 2.5%).

Baseline data

All participants in the microITT population had at least 1 Gram-positive (aerobic) pathogen from the ABSSSI site or blood at baseline. The most common pathogen was oxacillin-susceptible (MSSA) *S. aureus* identified in a total of 105 participants (84.0%), followed by *Streptococcus pyogenes* identified in 12 participants (9.6%), oxacillin-resistant (MRSA) *S. aureus* identified in 6 participants (4.8%), *Enterococcus faecalis* in 4 participants (3.2%), and *Streptococcus mitis/Streptococcus oralis* in 4 participants (3.2%). For all isolates that are considered label pathogens for dalbavancin, the MIC was at or below the EUCAST susceptible breakpoint (≤ 0.125 mg/L). No isolates were non-susceptible to dalbavancin, which is consistent with prior clinical trials in adult participants with ABSSSI. The MIC_{90} for *Staphylococcus aureus* was 0.06 µg/mL (both MSSA and MRSA).

Numbers analysed

Analysis populations (screened population)

Age Cohort Population	Dalbavancin Single-Dose	Dalbavancin Two-Dose	Comparator	Total
Overall				
Screened				204
ITT	90	78	30	198
mITT	84	78	30	192
Safety	90	78	30	198
CE-48-72H	83	75	30	188
CE-EOT	82	72	30	184
CE-TOC	82	72	30	184
CE-Follow-up	81	71	30	182
microITT	52	55	18	125
ME-48-72H	51	52	18	121
ME-EOT	50	50	18	118
ME-TOC	50	50	18	118
ME-Follow-up	49	49	18	116

Outcomes and estimation

The clinical response rate or cure rate was 90% or above as assessed by both the investigators and sponsor, in all treatment arms and across analysis populations. Clinical response at 48-72 hours (FDA recommended primary endpoint for efficacy studies in ABSSSI) and at later timepoints are tabled below. The proportion of clinical responders was generally similar across all age cohorts.

Ancillary analyses

Clinical response rates by baseline pathogen and microbiological response rates (generally presumed eradication based on lack of follow-up cultures) at different time-points and for different analysis populations were generally in line with the clinical response rates (data not shown). There have been no deaths in the study to date. Detailed subpopulation analyses were not performed as the patient numbers were not sufficient to support investigation of efficacy in subpopulations.

2.5.2. Discussion on clinical efficacy

This extension of indication application to include the paediatric population (aged 3 months to < 18 years) for the treatment of acute bacterial skin and skin structure infection (ABSSSI) relies on the concept of extrapolation of clinical efficacy and safety based on comparable plasma exposures in children to those in adults. The principle of extrapolation is endorsed and thus the descriptive nature of the efficacy data.

Design and conduct of clinical studies

Study DUR001-306 is a phase 3, multicentre, open-label, randomised, comparator-controlled trial of the safety and efficacy of dalbavancin versus active comparator in paediatric subjects with acute bacterial skin and skin structure infections. The study is still ongoing and continues to enrol participants in Cohort 5 (from birth to < 3 months) to satisfy European health authority requirements; currently 198 participants have enrolled. The study has included male and female paediatric patients from birth to 17 years of age with ABSSSI suspected or confirmed to be caused by Gram-positive bacteria, including MRSA. An alternative clinical picture of suspected or confirmed sepsis was also acceptable for the youngest age cohort (from birth to < 3 months). The infections had to be of sufficient severity to merit hospitalisation and parental antibacterial therapy.

The study compared single dose of IV dalbavancin or two doses of IV dalbavancin administered 1 week apart with a 10-to-14-day course of IV vancomycin (for infections caused by methicillin-resistant bacteria) or IV oxacillin or flucloxacillin (for infections caused by methicillin-susceptible bacteria) with an option to switch to oral treatment (cefadroxil or clindamycin) after at least 72 h of study drug treatment if they met criteria for oral therapy.

Efficacy objectives and endpoints were secondary and descriptive in nature including assessment of clinical response rate and clinical response rate by baseline pathogen at different timepoints and all-cause mortality at the test-of-cure visit 28 days after start of therapy (cohort 5 only [birth to <3 months]).

The sample size was not based on a power calculation for hypothesis testing. There was a 3:3:1 randomization scheme. The randomization scheme did not include the youngest age cohort (birth to < 3 months of age), as all 10 participants in this cohort were to receive the single-dose regimen of dalbavancin.

Efficacy analyses were based on the mITT Population (all randomized participants who received at least 1 dose of study drug and had a diagnosis of ABSSSI (or a suspected or confirmed sepsis for Cohort 5) not known to be caused exclusively by a Gram-negative organism) and specified CE, microITT, and ME populations. No statistical testing was planned for the efficacy endpoints.

The design of the study to primarily provide PK and safety data and descriptive efficacy data from paediatric patients with ABSSSI (or sepsis in case of the youngest cohort) was accepted. Overall, the design of the study to include a relevant study population for this purpose was endorsed.

Efficacy data and additional analyses

In total 198 subjects were included in the study (9 subjects aged form birth to < 3 months, 20 subjects aged 3 months to < 2 years, 45 subjects aged 2 years to < 6 years, 60 subjects aged 6 years to < 12years and 64 subjects aged 12 years to 17 years). The majority of study participants were male (62%) and white (88%). ABSSSI infection types were distributed on major cutaneous abscess 52%, cellulitis 29% and wound infection 19%.

All participants in the microITT population had at least 1 Gram-positive (aerobic) pathogen from the ABSSSI site or blood at baseline. The most common pathogen was oxacillin-susceptible (MSSA) *S. aureus* identified in a total of 105 participants (84.0%), followed by *Streptococcus pyogenes* identified in 12 participants (9.6%), oxacillin-resistant (MRSA) *S. aureus* identified in 6 participants (4.8%), *Enterococcus faecalis* in 4 participants (3.2%), and *Streptococcus mitis/Streptococcus oralis* in 4 participants (3.2%). For all isolates that are considered label pathogens for dalbavancin, the MIC was at or below the EUCAST susceptible breakpoint (≤ 0.125 mg/L). No isolates were non-susceptible to dalbavancin.

The clinical response rates at 48-72 hours were 96.4% (81/84), 98.6% (73/74) and 89.7% (26/29) in the dalbavancin single-dose, dalbavancin two-dose and comparator groups, respectively. At the TOC visit the response rates were above 90% in all treatment groups (95.1%, 97.3% and 100.0%, respectively). The response rates were essentially unchanged at the follow-up visit compared with at TOC.

Clinical response rates by baseline pathogen and microbiological response rates (generally presumed eradication based on lack of follow-up cultures) at different time-points and for different analysis populations were generally in line with the clinical response rates. There have been no deaths in the study to date. Detailed subpopulation analyses were not performed as the patient numbers were not sufficient to support investigation of efficacy in subpopulations.

Overall, the efficacy results from paediatric Study DUR001-306 are consistent with data from the adult Phase 3b Study DUR001-303.

DUR001-303 was a Phase 3b, double-blind, multicentre, randomised study to compare the efficacy and safety of single dose dalbavancin to a 2-dose regimen of dalbavancin for the treatment of ABSSSI. In each of the studies, the majority of participants were white with a higher percentage of male participants compared with female participants. Overall, *S. aureus* (MSSA and MRSA) was reported in 94.2% of participants in the dalbavancin single-dose group and 87.3% of participants in the dalbavancin 2-dose group in Study DUR001-306 and in 65.2% of participants in the dalbavancin single-dose group and 65.9% of patients in the dalbavancin 2-dose group in Study DUR001-303. MRSA was reported in a smaller number of participants (3.8% and 7.3% of participants in the dalbavancin single-dose and 2-dose groups respectively in Study DUR001-306, and 17.1% and 27.7% of participants in the dalbavancin single-dose and 2-dose groups respectively in Study DUR001-303.

In DUR001-306, the proportion of clinical responders at 48 to 72 hours, as assessed by the sponsor, was 96.4% in the dalbavancin single-dose arm and 98.6% in the dalbavancin 2-dose arm (mITT). Similarly, the proportion of clinical responders at 48 to 72 hours was 81.4% in the dalbavancin single-dose arm and 84.2% in the dalbavancin 2-dose arm (ITT) in Study DUR001-303. The clinical cure rate at the TOC visit (Day 28) in the mITT population in Study DUR001-306, as assessed by the sponsor, was 95.1% in the dalbavancin single-dose arm and 97.3% in the dalbavancin 2-dose arm (mITT). The clinical success rate at the Final Visit (Day 28) was 84.5% in the dalbavancin single-dose arm and 85.1% in the dalbavancin 2-dose arm (ITT) in Study DUR001-303.

2.5.3. Conclusions on the clinical efficacy

Clinical response rates in the paediatric ABSSSI study DUR001-306 were numerically comparable in dalbavancin single-dose, dalbavancin 2-dose and comparator groups, respectively, and moreover in line with the response rates in the adult study DUR001-303.

2.6. Clinical safety

Introduction

Studies contributing to the paediatric safety data are study DUR001-306 which is described in the efficacy section and the following studies:

DAL-PK-02

Study DAL-PK-02 was a multicentre, randomized, open-label, single-dose Phase 1 study in preterm neonates to infant ages < 3 months with suspected or confirmed bacterial infection. A total of 22 participants were planned to be enrolled in the following 3 cohorts: Cohort 1, young infants aged > 28 days to < 3 months; Cohort 2, term neonates (defined as gestational age ≥ 37 weeks) aged ≤ 28 days; Cohort 3, preterm neonates (defined as gestational age ≥ 32 to < 37 weeks) aged ≤ 28 days. However, due to difficulty in recruitment, and because participants in this age range were also being enrolled in Study DUR001-306 with a similar PK sampling schedule, enrolment was stopped in October 2019. The final enrolment included 8 participants, with 6 participants in Cohort 1, and 1 participant each in Cohorts 2 and 3. The dose for all participants was 22.5 mg/kg dalbavancin administered as a 30-minute IV infusion.

A8841004

Study A8841004, was an open-label, multicentre Phase 1 study designed to investigate the PK, safety and tolerability of a single dose of IV dalbavancin in 10 paediatric participants from 12 to 17 years of age receiving standard IV anti-infective treatment for bacterial infections. In this study, a single dose of 1000 mg dalbavancin was administered to participants weighing ≥ 60 kg and 15 mg/kg for participants weighing < 60 kg. The dose was given as a 30-minute IV infusion on Day 1.

DUR001-106

Study DUR001-106 was an open-label, single-dose Phase 1 study to investigate the PK, safety, and tolerability of dalbavancin in hospitalized children aged 3 months to 11 years receiving standard IV anti-infective treatment for bacterial infections. Participants in this study were enrolled and evaluated in 3 age cohorts: Cohort 1 (6 to 11 years of age), Cohort 2 (2 to < 6 years of age), and Cohort 3 (3 months to < 2 years of age). The planned dalbavancin doses were 15 mg/kg (not to exceed the adult dose of 1000 mg) for participants ≥ 5 years of age (n = 11), and 25 mg/kg for participants < 5 years of age (n = 7), administered as a 30-minute IV infusion on Study Day 1. After an interim PK analysis, the dosage for Cohort 3 (3 months to < 2 years of age) was reduced to 10 mg/kg.

Adult safety profile

The adverse effect profile of dalbavancin is essentially similar to those of other glycopeptides, with important exceptions: vancomycin and teicoplanin are both associated with nephrotoxicity and ototoxicity; dalbavancin on the other hand, has not clearly been associated with such toxicities at the proposed dose regimen.

The most common adverse reactions in the adult development programme occurring in ≥ 1 % of patients treated with dalbavancin were nausea (2.4 %), diarrhoea (1.9 %), and headache (1.3 %) and were generally of mild or moderate severity. Important identified risks in the Summary of the safety concerns in the Risk Management plan (tabled below) includes emergence of resistance, pseudomembranous colitis and hypersensitivity. Important potential risks include hepatic disorder, otovestibular toxicity, nephrotoxicity and haematological effects. There are no ongoing additional pharmacovigilance activities to characterize these risks further. Moreover, there are no ongoing additional risk minimisation measures for

any of the safety concerns. Routine risk minimisation measures are considered sufficient to manage these 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

Patient exposure

Cumulative exposure

The clinical experience with dalbavancin includes subjects in 28 completed Phase 1 to 3 clinical studies and adult participants have been exposed to dalbavancin in the post marketing setting. The clinical study program (completed and ongoing studies) consists of 4511 healthy participants and participants with infections who have been enrolled and received study medication, of which 3123 were treated with dalbavancin and 1388 were treated with a comparator (1316 active comparator and 72 placebo).

Exposure in paediatric participants

In Study DUR001-306, 198 participants were enrolled as of 21 June 2021, including 90 in the dalbavancin single-dose arm and 78 in the dalbavancin 2-dose arm. All 198 of these participants finished the study as of 05 November 2020, and their data has been locked. However, the study is ongoing to enrol more participants in Cohort 5 to satisfy European healthy authority requirements.

In Study DAL-PK-02, 8 paediatric participants were enrolled and received dalbavancin (single dose of 22.5 mg/kg dalbavancin as a 30-minute IV infusion): 6 participants in Cohort 1 (young infants aged > 28 days to < 3 months) and 1 participant each in Cohort 2 (term neonates [defined as gestational age ≥ 37 weeks] aged ≤ 28 days) and Cohort 3 (preterm neonates [defined as gestational age ≥ 32 to < 37 weeks] aged ≤ 28 days).

In Study A8841004, 10 paediatric participants from 12 to 17 years of age were enrolled and received a single dose of 1000 mg dalbavancin (participants weighing ≥ 60 kg; n = 5) or 15 mg/kg for (participants weighing < 60 kg, n = 5); the dose was administered as a 30-minute IV infusion.

In Study DUR001-106, 34 paediatric participants received treatment. Participants in this study were enrolled and evaluated in 3 age cohorts: Cohort 1 (6 to 11 years of age; n = 11), Cohort 2 (2 to < 6 years of age; n = 12), and Cohort 3 (3 months to < 2 years of age; n = 11). The planned dalbavancin doses were 15 mg/kg (not to exceed the adult dose of 1000 mg) for participants ≥ 5 years of age, and 25 mg/kg for participants < 5 years of age, administered as a 30-minute IV infusion on Study Day 1. After an interim PK analysis, the dosage for Cohort 3 (3 months to < 2 years of age) was reduced to 10 mg/kg.

Adverse events

DUR001-306

Eight (8.9%) participants in the dalbavancin single-dose arm, 7 (9.0%) in the dalbavancin 2-dose arm, and 1 (3.3%) in the comparator arm experienced a treatment-emergent adverse event (TEAE). TEAEs that occurred in more than 1 participant overall were pyrexia and cough (each in 2 participants in the dalbavancin 2-dose arm), nasopharyngitis (1 participant in the dalbavancin single-dose arm and 1 in the comparator arm), and postoperative anaemia (1 participant in the dalbavancin 2-dose arm and 1 in the comparator arm). No treatment-related TEAEs were reported in the study. Most TEAEs were mild or moderate in severity. Three SAEs were reported, all in the dalbavancin single-dose arm of which none were considered treatment-related.

DAL-PK-02

In total, 36 AEs were reported during the study; 35/36 were TEAEs. Six participants had TEAEs, all in Cohort 1. No TEAEs were reported in Cohorts 2 and 3. The most commonly reported TEAEs in DAL-PK-02 were pyrexia (3 [37.5%] participants) and procedural pain (2 [25.0%] participants); all in Cohort 1. All other TEAEs were reported as single instances.

A8841004

In study A8841004 which enrolled paediatric subjects aged from 12 to 17 years, headache, experienced by 1 participant in each dose group, was the only AE to be experienced by more than 1 participant. All other TEAEs in both groups were reported as single instances.

DUR001-106

In total, 39 AEs were reported during the study; 36/39 were TEAEs. There was a total of 9 TEAEs in Cohort 1, 23 in Cohort 2, and 4 in Cohort 3, occurring in 6 (54.4%), 9 (75.0%), and 4 (36.4%) participants, respectively. The following TEAEs were reported in 2 participants across all cohorts in Study DUR001-106: acoustic stimulation tests abnormal; acute respiratory failure; audiogram abnormal, dermatitis diaper; and pruritus. All other TEAEs in all cohorts were reported as single instances.

Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in the DUR001-306, DAL-PK-02, A8841004, or DUR001-106 studies.

SAEs

Three treatment-emergent SAEs were reported in Study DUR001-306, all in the dalbavancin single-dose arm (bacterial abscess, febrile convulsion and bacterial osteomyelitis) which all recovered/resolved and were considered unrelated to study intervention.

In study DAL-PK-02, one participant experienced treatment-emergent SAEs (necrotizing colitis and hydrocephalus). The SAE of necrotizing enterocolitis was reported as resolved and considered unrelated to dalbavancin as the participant had a history of pneumatosis intestinalis on abdominal ultrasound prior to dalbavancin administration. The SAE of hydrocephalus was ongoing at the time of the final report and was considered by the investigator as unrelated to dalbavancin as the participant had a history of ventriculomegaly and severe meningitis/ventriculitis.

In study A8841004, one SAE, mild ileus, was reported from 1 participant in the 15 mg/kg group. This SAE was considered by the investigator to be related to complications following an intra-abdominal abscess and not related to treatment. The participant recovered the day after onset of the event.

In study DUR001-106, five participants had SAEs (abdominal pain, arthralgia, device-related sepsis, abdominal abscess and acute respiratory failure) which all recovered/resolved and were considered unrelated to study intervention.

Other significant events

Audiologic testing has been conducted in a total of 18 participants in study DUR001-306 (1 in the 3-month to < 2-year 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). Of the 18 participants, 14 received dalbavancin and 4 received comparator (3 in the 6-year to <12-year cohort and 1 in the 12-year to 17-year cohort). Review of the audiology parameters at baseline and Day 28 in all participants (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.

Audiology testing was performed in 8 participants aged birth to <3 months in study DAL-PK-02 Due to the age and underlying illness of participants in the study, audiology testing was difficult to perform and interpret in the cohorts that were studied. Despite these limitations, there was no evidence of ototoxicity due to dalbavancin in participants for whom results were obtained and evaluable.

In study DUR001-106, audiology testing was performed in 34 participants (11 in the 3-month to <2-year cohort, 12 in the 2-year to <6-year cohort; 11 in the 6-year to <12-year cohort). Of the 34 participants, 21 (62%) had no evidence of ototoxicity due to dalbavancin and in 13 (38%) ototoxicity due to dalbavancin could not be determined.

Laboratory findings

Laboratory changes reported in DUR001-306 were consistent with the reduction in systemic immune response. There were no clinically significant mean changes in other laboratory parameters or vital signs.

Overall, in the paediatric studies there were very few and isolated potentially clinically significant changes in clinical laboratory values.

Discontinuation due to adverse events

There were no AEs leading to discontinuation of study intervention in any of the studies.

Post marketing experience

The cumulative number of vials distributed/sold of dalbavancin worldwide through 21 June 2021 is 523,769. This equates to an estimated post-authorization exposure of approximately 174,590 adult patients cumulatively.

The adverse reactions identified based on post marketing experience include hypersensitivity (including angioedema as a manifestation), anaphylactic reaction, and back pain (symptom of infusion-related reactions). Back pain occurred during dalbavancin IV infusion and resolved when the infusion was slowed down or discontinued, with no residual sequela.

2.6.1. Discussion on clinical safety

Studies contributing paediatric safety data are the Phase 3 study DUR001-306 and the Phase 1 studies DAL-PK-02, A8841004 and DUR001-106. Safety data were reported separately for the respective studies which is acceptable.

In Study DUR001-306, 198 participants were enrolled as of 21 June 2021, including 90 in the dalbavancin single-dose arm and 78 in the dalbavancin 2-dose arm. The proposed paediatric dosing provides slightly lower but largely overlapping exposure as in adults. Thus, from a safety perspective, similar or slightly lower exposure is not a concern. In Study DAL-PK-02, 8 paediatric participants were enrolled and received dalbavancin (single dose of 22.5 mg/kg dalbavancin): 6 participants in Cohort 1 (young infants aged > 28 days to < 3 months) and 1 participant each in Cohort 2 (term neonates [defined as gestational age ≥ 37 weeks] aged ≤ 28 days) and Cohort 3 (preterm neonates [defined as gestational age ≥ 32 to < 37 weeks] aged ≤ 28 days). In Study A8841004, 10 paediatric participants from 12 to 17 years of age were enrolled and received a single dose of 1000 mg dalbavancin (participants weighing ≥ 60 kg; n = 5) or 15 mg/kg for (participants weighing < 60 kg, n = 5). In Study DUR001-106, 34 paediatric participants received treatment. Participants in this study were enrolled and evaluated in 3 age cohorts: Cohort 1 (6 to 11 years of age; n = 11), Cohort 2 (2 to < 6 years of age; n = 12), and Cohort 3 (3 months to < 2 years of age; n = 11). The planned dalbavancin doses were 15 mg/kg (not to exceed the adult dose of 1000 mg) for participants ≥ 5 years of age, and 25 mg/kg for participants < 5 years of age. After an interim PK analysis, the dosage for Cohort 3 (3 months to < 2 years of age) was reduced to 10 mg/kg.

In study DUR001-306 dalbavancin received as a single or repeat intravenous infusion was generally well tolerated.

Overall safety findings from the DAL-PK-02, A8841004, and DUR001-106 studies were consistent with that reported for DUR001-306.

In summary, no new risks were identified as compared to the safety profile established in adults. It should be noted that the paediatric safety database, although acceptable, is of limited size to detect adverse reactions that are uncommon or rare. Overall, there were no findings needing to be reflected in the SmPC.

2.6.2. Conclusions on clinical safety

Dalbavancin administered as a single dose or two doses one-week apart resulting in an exposure essentially similar to that in adults was generally well tolerated and safe. No new risks were identified. There was no indication that the safety profile in the paediatric population would be different from that established in adults.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted an updated RMP version with this application (Version 7.0), the following sections were updated:

- Module SI with Xydalba indication in paediatric (aged 3 months and older) patients for the treatment of

acute bacterial skin and skin structure infections (ABSSSI). Also, prevalence of target population, demographic profile of target population, potential health risks in paediatric patients were updated. Information about important co-morbidities (diabetes mellitus, decreased renal function) in paediatric patients was also updated.

- Module SIII was updated with the latest overall clinical trial exposure numbers (exposure number updated from 3097 to 3123 persons) and also in paediatric population.

- Module SIV was updated with the frequency of adverse events seen in the studies DUR001-306, DAL-PK-02 and A8841004.

- Module SV was updated with the latest estimated post-authorisation exposure numbers (cumulative estimates calculated to 21 June 2021). Based on these sales data, an estimated 523,769 vials were distributed cumulatively, which the MAH has equated to be 174,589 patients exposed.

- Module SVII was updated with the information about three phase 1 completed studies (DUR001-106, DUR001-109 and DUR001-303) and with the latest post-marketing experience data, as summarised below.

The MAH did not propose changes to the Safety Specification. There are no new or removed safety concerns or reclassification of safety concerns during this RMP revision period. With this submission, no changes to PhV activities or risk minimisations are proposed.

Safety concerns

Details of important identified risks, important potential risks, and missing information
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. 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).

Important Identified Risk

Emergence of resistance

Cumulatively until the DLP, there have been 56 postmarketing cases which met search criteria for the important identified risk emergence of resistance. Of these 56 cases, 14 were considered serious. The case level outcomes of these serious cases were Unknown (6), Fatal (4), NA (3), 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.

Pseudomembranous colitis

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).

Hypersensitivity

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).

Important Potential Risk

Hepatic disorders

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).

Otovestibular toxicity

Cumulatively until the DLP, there have been 2 postmarketing cases reporting Otovestibular toxicity. There were no cases that were assessed as serious.

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.

Nephrotoxicity

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).

Haematologic Effects

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).

Missing information

Paediatric use

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/1.73m2 and above is a single-dose regimen based on the age and weight of the paediatric patient, administered as a single infusion.

According to the MAH, 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.

Summary of the 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

Pharmacovigilance plan

Summary table of additional pharmacovigilance activities

Table 42. Table of completed studies/activities from the pharmacovigilance plan

Activity/Study title (type of activity, study title [if known] 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	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

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PMR. Study also includes isolates collected from medical centers in Europe. Category 3				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

The MAH has updated the RMP to version 7.1 during this procedure to address a difference in the number of cases included for the PT Cellulitis and for the cases of otovestibular toxicity.

The PRAC considered that the risk management plan version 7.1 is acceptable.

The CHMP endorsed this advice without changes.

Risk minimisation measures

There are no ongoing additional pharmacovigilance activities to characterize these risks further. Moreover, there are no ongoing additional risk minimisation measures for any of the safety concerns. Routine risk minimisation measures are considered sufficient to manage these concerns.

Changes to the SmPC were agreed with this application, which adequately reflect the data submitted with the application.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guidelines and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend some of the contact details.

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xydalba. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

ABSSSI is a bacterial infection of the skin and skin structures and includes major cutaneous abscesses, wound infection and cellulitis/erysipelas. The most common causative pathogens are Staphylococcus aureus and various types of streptococci such as beta-haemolytic streptococci of groups A, B, C, and G. ABSSSI are among the most common infections seen in clinical practice in adults and in children. These infections may require systemic antibacterial therapy, surgical management and hospitalisation.

3.1.2. Available therapies and unmet medical need

There is a need for making new antibacterial agents available also to the paediatric population that will effectively treat infections caused by Gram-positive bacteria including resistant pathogens such as methicillin-resistant S. aureus.

3.1.3. Main clinical studies

Study DUR001-306 is an ongoing phase 3, multicentre, open-label, randomised, comparator-controlled trial of the safety and efficacy of dalbavancin versus active comparator in paediatric subjects with ABSSSI. The study continues to enrol participants in Cohort 5 (from birth to < 3 months) to satisfy European health authority requirements; currently 198 participants have enrolled. The study included paediatric patients from birth to 17 years of age with ABSSSI suspected or confirmed to be caused by Gram-positive bacteria. A clinical picture of suspected or confirmed sepsis was also acceptable for Cohort 5.

The study compared single dose of IV dalbavancin or two doses of IV dalbavancin administered 1 week apart with a 10-to-14-day course of IV vancomycin (for infections caused by methicillin-resistant bacteria) or IV oxacillin or flucloxacillin (for infections caused by methicillin-susceptible bacteria) with an option to switch to oral treatment (cefadroxil or clindamycin) after at least 72 h of study drug treatment if they met criteria for oral therapy.

Efficacy objectives and endpoints were secondary and descriptive in nature as the application relies on the concept of extrapolation of clinical efficacy and safety based on comparable plasma exposures in children to those in adults. The acceptance of extrapolation is based on assumptions that the disease, mechanism of action and thus PK/PD are the same in paediatric patients as in adults and therefore the doses selected should achieve similar plasma exposures and probability of PK/PD target attainment (PTA) in children as in adults.

3.2. Favourable effects

The proposed paediatric dosing provides slightly lower but largely overlapping exposure as in adults. The MAH discussed that the slightly lower exposure is not clinically relevant with regards to efficacy based on probability of target attainment analyses (PTA). This was accepted.

The clinical response rates at 48-72 hours were 96.4% (81/84), 98.6% (73/74) and 89.7% (26/29) in the dalbavancin single-dose, dalbavancin two-dose and comparator groups, respectively (mITT Population, i.e. all randomized participants who received at least 1 dose of study drug and had a diagnosis of ABSSSI, or a suspected or confirmed sepsis for Cohort 5, not known to be caused exclusively by a Gram-negative organism). At the TOC visit the response rates were above 90% in all treatment groups (95.1%, 97.3% and 100.0%, respectively). The response rates were essentially unchanged at the follow-up visit compared with at TOC.

Clinical response rates by baseline pathogen and microbiological response rates (generally presumed eradication based on lack of follow-up cultures) at different time-points and for different analysis populations were generally in line with the clinical response rates. There have been no deaths in the study to date.

3.3. Uncertainties and limitations about favourable effects

The primary objectives of the Phase 3 study were to evaluate PK and safety of dalbavancin in the paediatric population. Hence, the study was not powered for a statistical analysis of efficacy and of limited size.

3.4. Unfavourable effects

Studies contributing to paediatric safety data are the Phase 3 study DUR001-306 and the Phase 1 studies DAL-PK-02, A8841004 and DUR001-106. Safety data were reported separately for the respective studies which is acceptable.

In Study DUR001-306, 198 participants were enrolled, including 90 in the dalbavancin single-dose arm and 78 in the dalbavancin 2-dose arm. The proposed paediatric dosing provides slightly lower but largely overlapping exposure as in adults. Thus, from a safety perspective, similar or slightly lower exposure is not a concern.

In study DUR001-306 dalbavancin received as a single or repeat intravenous infusion was generally well tolerated. Overall, 8 (8.9%) participants in the dalbavancin single-dose arm, 7 (9.0%) in the dalbavancin 2-dose arm, and 1 (3.3%) in the comparator arm experienced a TEAE. TEAEs that occurred in more than 1 participant overall were pyrexia and cough (each in 2 participants in the dalbavancin 2-dose arm), nasopharyngitis (1 participant in the dalbavancin single-dose arm and 1 in the comparator arm), and postoperative anaemia (1 participant in the dalbavancin 2-dose arm and 1 in the comparator arm). No treatment-related TEAEs were reported in the study. Most TEAEs were mild or moderate in severity. Three SAEs were reported, all in the dalbavancin single-dose arm of which none were considered treatment-related. There were no AEs leading to discontinuation of study intervention or study, and no SAEs leading to death. Laboratory changes and vital signs were consistent with the reduction in systemic immune response. There were no clinically significant mean changes in other laboratory parameters or vital signs. Audiologic testing did not reveal any signal of ototoxicity.

Overall, safety findings from the Phase 1 studies DAL-PK-02, A8841004, and DUR001-106 were consistent with that reported for DUR001-306.

3.5. Uncertainties and limitations about unfavourable effects

The paediatric safety database, although acceptable, was of limited size to detect adverse reactions that are uncommon or rare.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

This extension of indication application to include the paediatric population (aged 3 months to < 18 years) for the treatment of acute bacterial skin and skin structure infection (ABSSSI) relied on the concept of extrapolation of clinical efficacy and safety based on comparable plasma exposures in children to those in adults. The approved dose in paediatric patients aged from 6 years to less than 18 years is a single dose of 18 mg/kg (maximum 1,500 mg) and in paediatric patients aged from 3 months to less than 6 years a single dose of 22.5 mg/kg (maximum 1,500 mg).

No dose reduction is recommended in mild or moderate renal impairment whereas there is according to the MAH insufficient information to recommend dosage adjustment for patients younger than 18 years with creatinine clearance less than 30 ml/min/1.73 m^2. The MAH elaborated on a dosing recommendation at least for a subset of the paediatric population with creatinine clearance less than 30 ml/min/1.73 m^2 and provided simulations results indicating a dose reduction of 25-33% in paediatric patients with severe renal impairment (similar to adults). However, given the lack of data in paediatric patients with severe renal impairment, the MAH believed there was insufficient information to recommend a dose regimen for paediatric patients in any age group with CrCL < 30 ml/min/1.73 m^2. The MAHs reasoning was accepted, and the following recommendation was added to section 4.2 of the SmPC for paediatric patients with renal impairment: "*There is insufficient information to recommend dosage adjustment for patients younger than 18 years with creatinine clearance less than 30 ml/min/1.73 m2. Currently available information is described in section 5.2, but no recommendation on a posology can be made*." The PL was updated accordingly. Information regarding the pharmacokinetics of dalbavancin in paediatric patients was added to section 5.2 of the SmPC.

The MAH did not propose to include the alternative two-dose regimen for the paediatric population in the SmPC which was accepted as there is no added benefit of having the option of using a two-dose regimen.

Based on essentially similar exposure in the paediatric population as in adults and satisfactory PTA it is anticipated that the recommended paediatric doses will be effective and safe in the paediatric population.

Clinical response rates in the paediatric ABSSSI study DUR001-306 were numerically comparable in dalbavancin single-dose, dalbavancin two-dose and comparator groups, respectively, and moreover in line with the response rates in the adult study DUR001-303.

Dalbavancin administered as a single dose or two doses one-week apart, resulting in an exposure essentially similar to that in adults was generally safe and well tolerated. No new risks were identified. There was no indication that the safety profile in the paediatric population would be different from that established in adults.

Regarding the claim for an additional year of market protection submitted by the MAH, data supporting the clinical benefits of dalbavancin for the treatment of paediatric patients with ABSSSI from the Phase 3

study DUR001-306 demonstrated favourable clinical and microbiological response rates across all participants regardless of dalbavancin dose regimens or age cohorts and did not vary significantly versus comparator treatments (IV vancomycin, oxacillin, or flucloxacillin). Consistent with that reported in adults, safety and tolerability were acceptable and comparable to comparator treatments overall across age and dose. No compound-specific or unique toxicity was identified, and, overall, the duration of AEs was similar to that of comparators. The pharmacokinetic properties of dalbavancin, allowing for a single-dose regimen, are considered of significant clinical benefit because of the reduced dosing frequency allowing a single-dose regimen compared with existing therapies for which repeated administration for several days is necessary.

3.7.2. Balance of benefits and risks

The balance of benefits and risk for the extension of indication of treatment of ABSSSI to include paediatric patients aged 3 months and older is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Xydalba is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considered the following variation acceptable and therefore recommended, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to the paediatric population (aged 3 months to < 18 years) for the treatment of ABSSSI based on the interim results from the safety and efficacy Phase 3 Study DUR001-306, together with data from three Phase 1 PK studies (A8841004, DUR001-106, and DAL-PK-02). Consequently, the sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC were updated. The Package Leaflet has been updated accordingly.
In addition, the MAH has taken the opportunity to make minor editorial amendments and QRD updates (v10.2) to the SmPC/PL.
Version 7.1 of the RMP has also been approved.

The MAH also requested 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0522/2021 (and subsequent modifications thereof) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).