



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 March 2025
EMA/127606/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Xydalba

International non-proprietary name: dalbavancin

Procedure No. EMEA/H/C/002840/II/0050

Note

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



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List of abbreviations

ABSSSI	acute bacterial skin and skin structure infection(s)
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AUC	area under the plasma concentration versus time curve
AUC ₀₋₁₂₀	area under the plasma concentration versus time curve from 0 to 120
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
CrCl	creatinine clearance
CSR	clinical study report
cSSSI	complicated skin and skin structure infection
CV	coefficient of variation
DAL-PK-02	also known as DUR001-107
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
GRE	glycopeptide-resistant Enterococci
HA	health authority(ies)
ICH	International Council for Harmonisation
ITT	intent-to-treat
IV	intravenous(ly)
LFU	late follow-up
MAA	Marketing Authorisation Application

MAH	Marketing Authorisation Holder
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
MIC90	minimum concentration that inhibits growth of 90% of isolates examined
microITT	microbiological ITT
mITT	modified intent-to-treat
PAMS	post-authorisation measures
PD	pharmacodynamic
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
PMR	post marketing requirement
PTA	PK/PD target attainment
SAE	serious adverse event
SSSI	skin and skin structure infection
TEAE	treatment-emergent adverse event
TOC	test of cure (visit)
ULN	upper limit of normal
US	United States
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 31 May 2024 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, IIIA and IIIB

Extension of indication to include the treatment of acute bacterial skin and skin structure infections (ABSSSI) in paediatric patients from birth, including paediatric patients aged less than 3 months with suspected or confirmed sepsis associated with skin and subcutaneous tissue infections for Xydalba, based on final results from study DUR001-306, together with data from three Phase 1 PK studies (A8841004, DUR001-106, and DUR001-107 (DAL-PK-02); DUR001-306 was a 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. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet in line with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0467/2023 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP was completed. The PDCO issued an opinion on compliance for the PIP.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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.

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	31 May 2024
Start of procedure:	14 September 2024
CHMP Rapporteur Assessment Report	6 November 2024
PRAC Rapporteur Assessment Report	15 November 2024
PRAC members comments	20 November 2024
Updated PRAC Rapporteur Assessment Report	21 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	2 December 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	5 December 2024
Request for supplementary information (RSI)	12 December 2024
CHMP Rapporteur Assessment Report	25 February 2025
PRAC Rapporteur Assessment Report	4 March 2025
PRAC members comments	5 March 2025
Updated PRAC Rapporteur Assessment Report	7 March 2025
PRAC Outcome	13 March 2025
CHMP members comments	17 March 2025
Updated CHMP Rapporteur Assessment Report	20 March 2025
Opinion	27 March 2025

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. The indication was already extended on 9 February 2022 to include the paediatric population aged 3 months to < 18 years. This application is a further extension of the indications to propose inclusion of the full paediatric population.

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.

2.1.1. Problem statement

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. 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*.

Claimed therapeutic indication

The proposed wording for the extended therapeutic indications was (proposed addition in ***bold italics*** and deletions in ~~strikethrough~~):

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~~ ***from birth***.

2.1.2. 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.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

An ERA document for dalbavancin (Xydalba), dated May 2024, was submitted with this variation application (the previous ERA was dated July 2022). In it, is noted that Xydalba has previous approval for ≥ 3 months patient populations.

The previous ERA approved a Log Kow of 2.3 (not triggering a PBT assessment). The default PEC_{sw} value was calculated using a maximum daily dose of 4.11 mg/day and the default F_{pen} value of 0.01, resulting in a Phase I PEC_{sw} value of 0.000021 mg/L (0.021 µg/L). As the PEC_{sw} value exceeded 0.01 µg/L, a refined PEC_{sw} value was calculated using a F_{pen}-actual obtained from recent epidemiology studies on ABSSSI. Based on a publication by Godbout (2013) and Grossi et al. (2022) one got several refined F_{pen}

values, the most conservative being 0.00327 representing the prevalence in Germany from data for 2024. Using the max dose of 4.11 mg/d and the F_{pen} of 0.00327, a prevalence-refined PEC_{sw} was calculated to 0.0000067 mg/L (0.0067 µg/L) and < 0.01 ug/L. This can be compared to the previous Xydalba® ERA which had a refined F_{pen} of 0.00311 and a Phase I PEC_{sw} of 0.0064 ug/L.

The MAH also provided a limited voluntary Phase IIA assessment for (sludge) microorganisms (which with an OECD TG209 derived PNEC of 22.7 mg/L gives a risk quotient of 0.00000029). This assessment is strictly speaking is not necessary as antibiotic drugs do not enter Phase II regardless of the Phase I PEC_{sw} action limit.

Considering the above data and setting aside the general concerns of spread of antibiotic drug resistance (which cannot be addressed with the ERA), dalbavancin is not expected to pose a risk to the environment.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted for this application. The absence of new experimental studies for this new age-interval is acceptable. The new age interval (<3 months) has not been discussed in a Non-clinical overview. The previous Non-clinical overview was provided during the original MAA and which included two juvenile rat toxicity studies (IV exposure at 5, 10 or 40 mg/kg, from postnatal day (PND) 7 and forwards which is a reasonable lowest age for toxicological exposure of rodent pups). In those studies, dalbavancin did not adversely affect sexual maturation or reproductive function in males or females, with a NOAEL for 8 weeks exposure at 10 mg/kg/day. The NOAEL for sexual maturation, mating and fertility was 40 mg/kg/day when given to neonatal rats from PND 7 through PND 63. There were some tendencies to dose accumulation over the exposure period (~2x-2.5x fold). All effects had either reversed or there was a trend toward reversal at the end of the recovery period. It can be noted that in previous approvals, the non-clinical assessment was put in context of a post-authorisation measure (PAM) of surveillance spanning 2014-2018.

Overall, the non-clinical part of the dossier is considered acceptable. It is unlikely that, based on the existing animal studies, novel toxicological concerns can be identified for the proposed age range <3 months compared to the previous accepted age range of 3 months to 6 years.

2.2.3. Conclusion on the non-clinical aspects

There are no non-clinical concerns regarding the approval of this procedure.

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

2.3. Clinical aspects

2.3.1. Introduction

This application for extending the indication to paediatric patients from birth to < 3 months relies on extrapolating efficacy from comparable dalbavancin plasma exposures between paediatric patients and adults.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH (see Table 1 below).

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.

- *Table 1 - tabular overview of clinical studies*

Study	Age and Cohorts	Type of Study	Design
DUR001-306	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 (or suspected/confirmed sepsis in participants less than 3 months old) 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 199 participants were enrolled, including 91 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 paediatric participants aged from 12 to 17 years of age receiving standard IV anti-infective treatment for bacterial infections.	Primary endpoints: PK parameters 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	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	Primary endpoints: PK parameters. 34 participants were assigned to study treatment and treated in 3 age cohorts: Cohort 1

Cohort 3: 3 months to < 2 years	the IV administration of a single dose of dalbavancin.	(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).
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DUR001-107 (DAL-PK-02)	Cohort 1: young infants age > 28 days to < 3 months	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.
	Cohort 2: term neonates (GA ≥ 37 weeks) aged ≤ 28 days		Planned number of participants: 22
	Cohort 3: preterm neonates (GA ≥ 32 to < 37 weeks) aged ≤ 28 days		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.
			Final enrolment: 8 participants (6 in Cohort 1 and 1 each in Cohorts 2 and 3)

2.3.2. Pharmacokinetics

The general pharmacokinetics of dalbavancin, including absorption, distribution, and elimination, are outlined in the assessment of the initial marketing authorisation application for Xydalba (EMA/H/C/002840/0000).

- **Bioanalytical methods**

The validated bioanalytical methods used in the clinical development programs were precise, accurate, and met acceptable assay validation criteria for all applications.

The CHMP noted that there is no new biopharmaceutical information in the current procedure and no new bioanalytical methods were used for the analysis of samples from the paediatric studies.

- **Pharmacokinetic data analyses**

The paediatric PK data were analysed using a PopPK approach.

Data

A total of 1 164 PK observations from 219 paediatric patients were included in the popPK model development. No observations from the newly added subjects were excluded. A summary of the number

of subjects in the analysis dataset by study and dose is provided in Table 2, and by study and age in Table 3.

Table 2. Number of subjects (%) in analysis dataset by dose and study.

Study	A8841004	DUR001-106	DUR001-107	DUR001-306	All
	(N = 10)	(N = 33)	(N = 8)	(N = 168)	(N = 219)
Dose					
10 mg/kg		11 (33.3%)			11 (5.0%)
12 mg/kg				53 (31.5%)	53 (24.2%)
15 mg/kg	10 (100.0%)	12 (36.4%)		22 (13.1%)	44 (20.1%)
18 mg/kg				54 (32.1%)	54 (24.7%)
22.5 mg/kg			8 (100.0%)	39 (23.2%)	47 (21.5%)
25 mg/kg		10 (30.3%)			10 (4.6%)
PK observation records					
Number of pre-dose BQL observations	10	0	0	0	10
Number of post-dose BQL observations	1 (0.8%)	0 (0%)	1 (2.1%)	16 (1.9%)	18 (1.5%)
Number of post-dose non-BQL observations	119	192	47	806	1164

One subject from Study DUR001-106 (102-209, NMID 11) and one subject from Study DUR001-306 (DUR001-306.30130601, NMID 79) were excluded from this summary table as all their PK observations were BQL.

The CHMP considered the data exclusion criteria and methods to be acceptable. A similar approach was also used in a previous Type II variation for extension of the paediatric indication (EMA/H/C/002840/II/0043).

Table 3. Number of subjects in analysis dataset by age group and study.

Age group	Number of subjects				
	A8841004	DUR001-106	DUR001-107	DUR001-306	All
Preterm neonate			1	2	3
Term neonate			1	4	5
28 days to < 3 months			6	4	10
3 months to < 2 years	11			16	28
2 to < 6 years	11			35	46
6 to < 12 years	11			49	60
12 to < 18 years	10			58	68

The new PK data since the previous paediatric Type II variation (EMA/H/C/002840/II/0043) comes from the now completed Study DUR001-306, which includes 8 additional paediatric subjects: 2 pre-term, 1 term, 2 young infants (28 days to < 3 months), and 3 infants (3 months to < 2 years).

Figure 1 presents individual dalbavancin plasma concentration-time profiles on a semi-logarithmic scale, stratified by study and dosing regimen (single or two-dose).

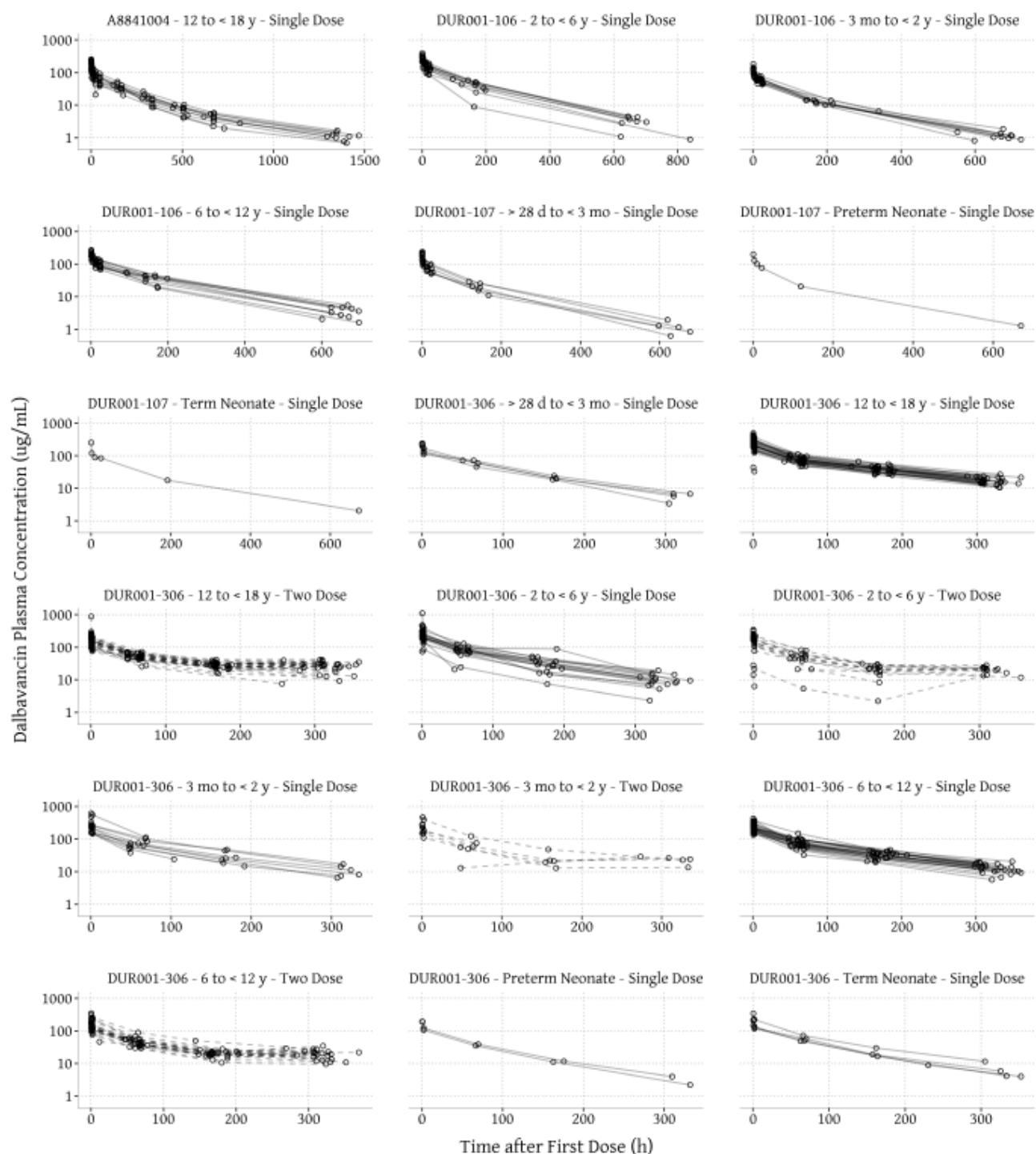


Figure 1. Dalbavancin plasma concentration versus time after first dose, by study and age group. A solid line represents single-dose data, and a dashed line represents two-dose data. Open circles represent observations.

Model

The current popPK model is a re-estimation of a previous paediatric popPK model which was submitted in a previous paediatric Type 2 variation (EMA/H/C/002840/II/0043), with the addition of eight paediatric patients < 2 years, where 2 are infants and 3 are neonates. Inclusion of covariates were reassessed, and final parameter estimates are given in Table 4. A pcVPC stratified by age group is included in Figure 2.

Table 4. Parameter estimates of the final popPK model

Parameter	Description	Units	Estimate	Bootstrap 95% CI
θ_1	CL	L/h	0.058	(0.0552 - 0.0608)
θ_2	V	L	4.62	(4.29 - 4.93)
θ_3	V2	L	6.16	(5.73 - 6.61)
θ_4	Q	L/h	0.805	(0.715 - 0.906)
θ_5	Q2	L/h	0.00998	(0.00898 - 0.0113)
θ_6	V3	L	5.59	(4.58 - 7.23)
θ_8	F1,ALB	-	0.396	(0.161 - 0.599)
θ_9	CL,EGFRN	-	0.135	(0.0243 - 0.231)
θ_{10}	CL,CLCRN	-	0.0691	(-0.0331 - 0.181)
$\omega_{1.1}$	IIV,CL	sd (CV%)	0.316 (32.4)	(0.255 - 0.388)
$\omega_{2.1}$	Corr,CL-V	-	0.812	-
$\omega_{2.2}$	IIV,V	sd (CV%)	0.452 (47.6)	(0.321 - 0.589)
$\omega_{3.1}$	Corr,CL-V2	-	0.853	-
$\omega_{3.2}$	Corr,V-V2	-	0.666	-
$\omega_{3.3}$	IIV,V2	sd (CV%)	0.322 (33.1)	(0.246 - 0.424)
$\sigma_{1.1}$	PropErr	sd	0.123	(0.0936 - 0.159)
$\sigma_{3.3}$	PropErr-PhIII	sd	0.171	(0.141 - 0.198)

The standardized reference weight of 70 kg was used in the allometric scaling of all disposition parameters, with fixed allometric exponents of 0.75 for all clearances (CL and Q) and 1 for all volumes. CI, confidence interval; ω_x , variance of the IIV of parameter X, IIV as a %CV was derived from variance according to $\sqrt{e^{\omega_x} - 1} \times 100$. Covariances are reported as correlations between the indicated parameters. Median and 95%CI calculated from a 1000-sample bootstrap, with 972 successful minimizations.

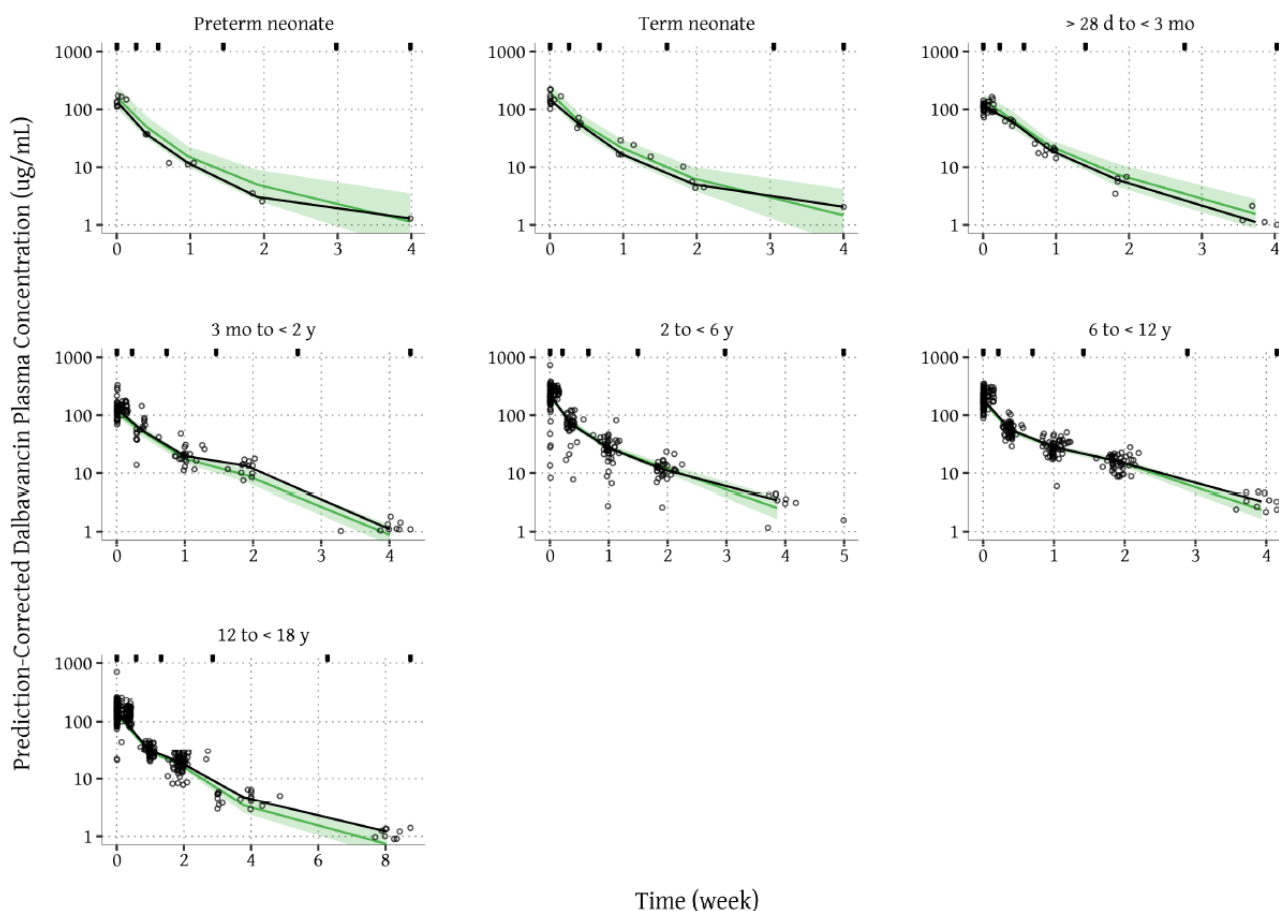


Figure 2. Prediction-Corrected Visual Predictive Check by Age Group Circles represent observed dalbavancin concentrations. The solid black line shows the median of observed values, while the solid green line shows the median of simulated concentrations. The green shaded area represents the 95% confidence interval around the prediction-corrected simulated median.

The CHMP considered that the parameter estimates from the final model appear reasonable. The pcVPC stratified on age group support that the model's predictive performance is satisfactory for all paediatric age groups including neonates, young infants, and infants.

Dose proportionality and time dependencies

Dalbavancin has been shown to exhibit dose-proportional PK given doses of 140–1 120 mg. The PD target associated with dalbavancin is $fAUC/MIC$, indicating no time-dependency for efficacious treatment.

Special populations

Renal impairment

The current paediatric analysis dataset did not contain dedicated renal impairment data, which is acceptable. The MAH therefore considered that there is insufficient information to recommend a dose regimen for paediatric patients with $CrCL < 30 \text{ mL/min/1.73m}^2$. This was acceptable to the CHMP.

Hepatic impairment

The current paediatric analysis dataset did not contain dedicated hepatic impairment data. Exposure stratified by hepatic impairment was thus not evaluated. The CHMP considered this to be acceptable.

Gender

Exposure stratified by gender was not evaluated, which the CHMP considered acceptable.

Race

Exposure stratified by race was not evaluated. The CHMP considered this to be acceptable.

Body weight

The simulated exposures (AUC_{0-120h}) across the body weights of paediatric subjects were generally comparable (Figure 3). Children with the lowest body weight, corresponding to preterm neonates, have the lowest exposures (dosing being weight-based).

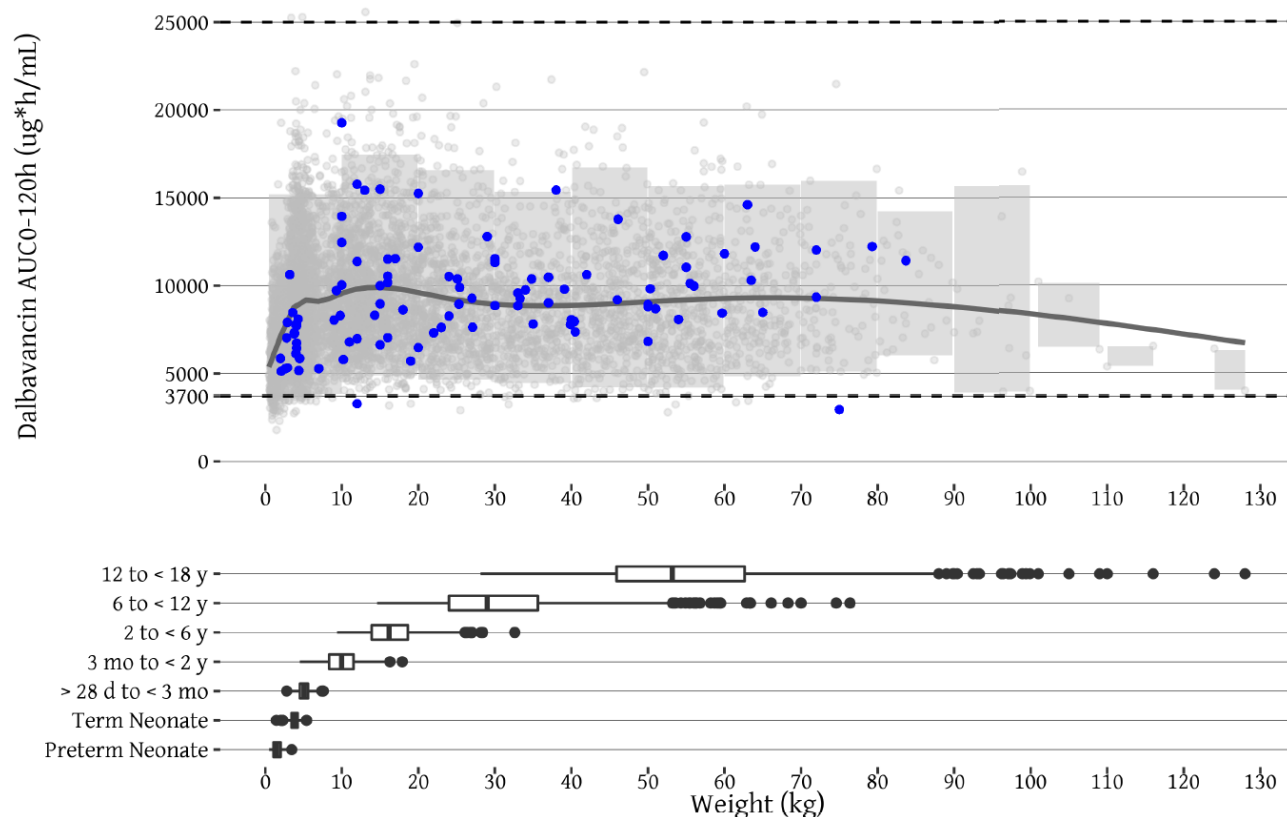


Figure 3. Simulated AUC_{0-120h} vs. body weight. Open circles: Simulated individual paediatric exposures. Shaded areas: 95% prediction intervals. Dashed lines: Adult exposure range from Phase 3. Blue circles: Post-hoc exposure estimates from DUR001-107 and DUR001-306. Solid line: LOESS smooth. Bottom panel box plots: Body weight distribution by age group.

Age

The simulated exposures (AUC_{0-120h}) across the age of paediatric subjects were generally comparable (Figure 4). The youngest children have the lowest exposures.

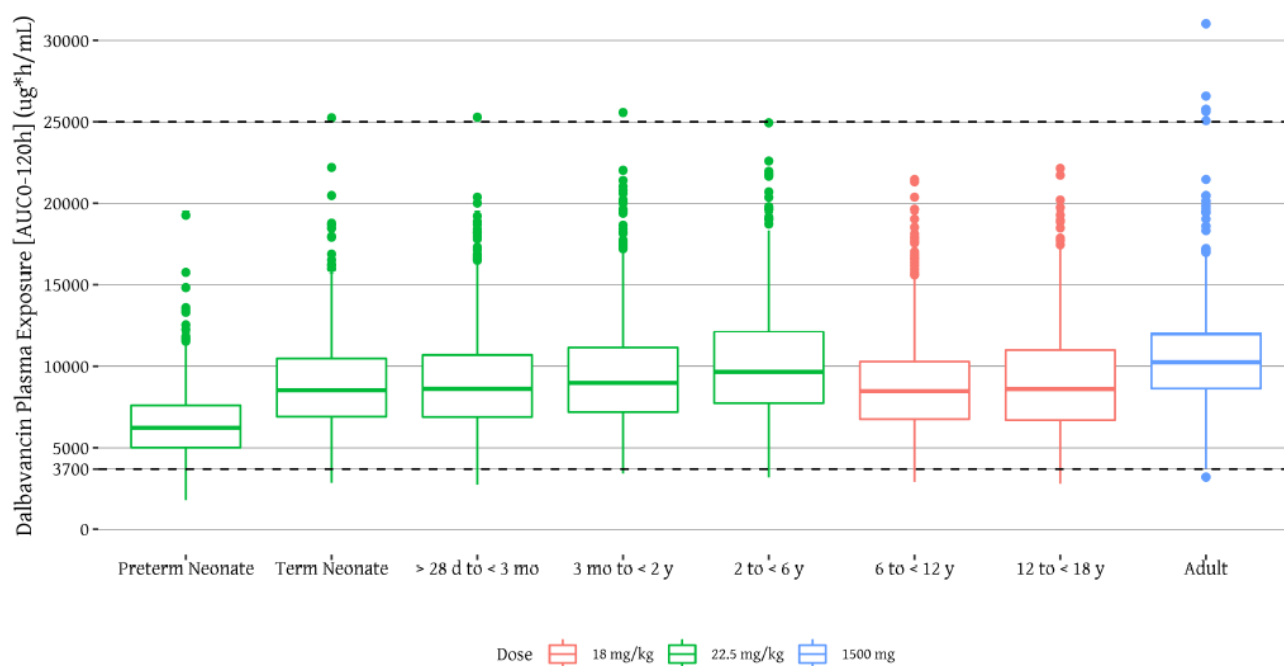


Figure 4. Box-and-whisker plot comparing simulated paediatric and adult AUC_{0-120h} . The plot shows the median (central line), interquartile range (box), and whiskers extending to $1.5 \times IQR$. Dots represent values outside the IQR. Dashed black lines indicate the adult AUC_{0-120h} range from Phase 3 after a single 1500 mg dose.

The CHMP considered that the box plots in Figure 4 demonstrate that all paediatric age groups achieve exposures compared to adults. Preterm neonates exhibit the lowest exposure but the exposure is generally within the adult exposure range, which was acceptable to the Committee.

Pharmacokinetic interaction studies

No new drug-drug interaction studies were submitted with this application.

Probability of target attainment

Target

Target attainment (TA) simulations were performed with the updated paediatric popPK model for the previously reported non-clinical dalbavancin $fAUC/MIC$ target for 2-log kill (111.1). The daily free dalbavancin exposure metric, ($fAUC_{avg}$), used for calculating probability of target attainment (PTA), was defined as $fAUC_{0-120}/5$, with the assumption of 93% of drug bound to albumin.

PTA - adults and paediatric patients

Figure 5 displays the 2-log kill PTA for all simulated age groups with respect to MIC values ranging from 0.002 to 16 $\mu g/mL$ and in relation to the MIC distributions for the four most relevant species of pathogens obtained in the JMI-analyzed microbial surveillance data from 2017. The comparison between the highest observed MICs (0.25 $\mu g/mL$) and the MIC where predicted PTA 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 Europe.

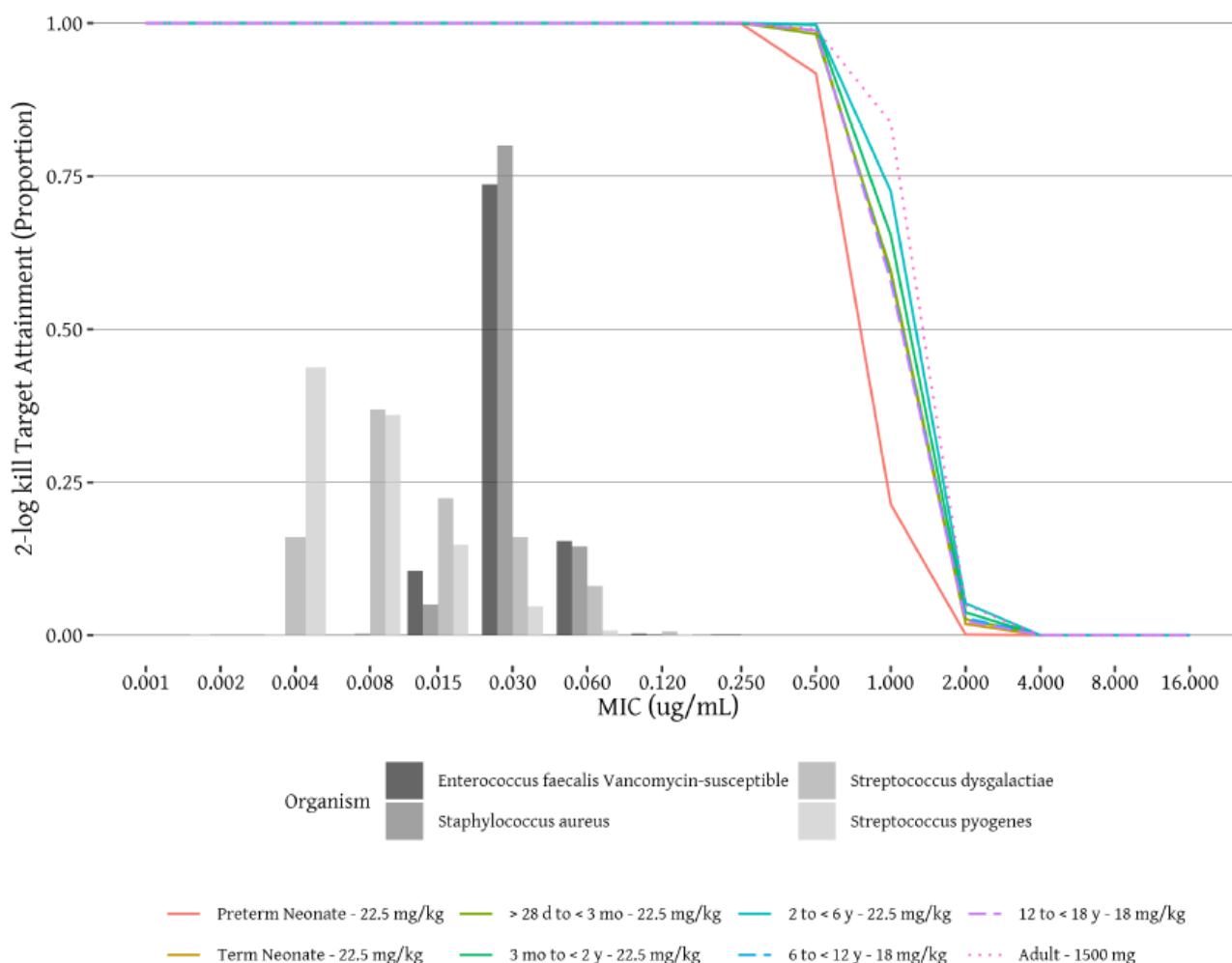


Figure 5. Simulated 2-log kill target attainment in paediatric and adult populations against 2017 surveillance MIC distributions for four key pathogens. The black and white histogram shows MIC distributions, while the coloured lines represent target attainment for age-specific dosing regimens. MIC: Minimal Inhibitory Concentration ($\mu\text{g/mL}$).

The CHMP considered that the simulated dalbavancin exposure in paediatric patients and adults largely overlapped. However, the exposure in pre-terms were slightly lower (but still within the adult target exposure range). PTA results for adults and paediatric patients, excluding preterm neonates, were similar. The PTA methodology—exposure metric, conservative 2-log-kill target, and revised target value— was considered acceptable (which is in line with the assessment of a previous paediatric Type 2 variation [EMA/H/C/002840/II/0043]).

The highest observed MICs (0.25 $\mu\text{g/mL}$) and the MIC where predicted PTA starts to decrease indicates that the dosing regimens would continue to provide attainment of the preclinical PK/PD target, even for preterm neonates, for at least up to a MIC of 0.5 mg/L which well includes the upper end of the MIC-distributions and EUCAST susceptibility breakpoints (0.125 mg/L) for relevant pathogens causing ABSSSI. Thus, this supports that the proposed dose is acceptable in all paediatric patients, including pre-term neonates.

2.3.3. Discussion on clinical pharmacology

This application to extend the indication to paediatric patients from birth to < 3 months is based on demonstrating comparable dalbavancin plasma exposures between paediatric patients and adults.

The analysis used 1 164 PK observations from 219 subjects, including new data from Study DUR001-306, which added eight paediatric subjects across various age groups (two preterm, one term, two young infants, and three infants). All subjects were retained in the dataset, with Table 2 and

Table 3 summarizing subjects by study, dose, and age.

The updated popPK model re-estimates the previous paediatric model by incorporating these new data, and covariate inclusion was re-evaluated. Final parameter estimates are in Table 4, and pcVPC results, stratified by age, confirm satisfactory predictive performance across paediatric groups (Figure 2).

The final PopPK model was used to support the proposed posology in paediatric patients using clinical trial simulations of PK exposure. Figure 4 demonstrates comparable exposures between paediatric and adult subjects, with preterm neonates showing the lowest exposure (weight-based dosing). All paediatric age groups achieve exposures compared to adults which means that the proposed posology is acceptable. Of note, preterm neonates exhibit the lowest exposure but the exposure is generally within the adult exposure range, which is acceptable.

Dalbavancin PK is dose-proportional for doses between 140–1 120 mg, with *f*AUC/MIC as the PD target, indicating time-independent efficacy.

The final PopPK was used to perform PTA simulations. Simulated dalbavancin exposures in paediatric patients generally align with adult exposure, achieving comparable probability of target attainment (PTA) across age groups, including preterm neonates. While exposures are slightly lower in preterm neonates, the proposed dosing meets PK/PD targets, with > 90% attainment across all age groups for the observed MIC distribution. Using a conservative PK/PD target of a 2-log kill, PTA analysis also indicates that this dose is adequate up to an MIC of 0.5 mg/L. This coverage extends beyond the maximum observed MIC (0.25 µg/mL) and EUCAST susceptibility breakpoints (0.125 mg/L) for relevant pathogens causing ABSSSI. Thus, this further supports that the proposed dose is acceptable in all paediatric patients, including preterm neonates.

The renal function cutoff of CRCL ≥ 30 mL/min/1.73 m² for dose recommendations may not be suitable for the sought paediatric population. Thus, it is appropriate to state in the SmPC that the renal impairment in patients <3 months can be defined as serum creatinine ≥ 2 times the upper limit of normal, or urine output < 0.5 mL/kg/h, or requirement for dialysis. This is in line with studies DUR001-306 and DUR001-007 where subjects <3 months with moderate or severe renal impairment were excluded, defined as *"serum creatinine ≥ 2 times the upper limit of normal ($\times$ ULN) for age OR urine output < 0.5 mL/kg/h (measured over at least 8 hours prior to dosing) OR requirement for dialysis"*.

The MAH added information in SmPC section 5.2 about renal function in patients < 3 months specifying the normalised creatinine clearance range of 34 to 118 mL/min/1.73m² using the Schwartz bedside equation, which is acceptable. During the assessment, the MAH was asked to resolve minor issues in Sections 4.2, 4.4 and 5.2 related to renal impairment in children <3 months for the SmPC to be acceptable. The MAH agreed to the wording recommendations and provided Product Information documents amended accordingly.

2.3.4. Conclusions on clinical pharmacology

The PopPK model used to describe PK in paediatric patients is acceptable. The PopPK model was used to support the proposed dose in all relevant groups by clinical trial simulations. The PK simulations

demonstrated overall comparable exposure between children and adults. Preterm neonates had slightly lower exposures but were within the adult target exposure range. Clinical trial simulations also include PTA simulations which demonstrated acceptable PTA in all relevant age groups. Thus, the proposed dose is considered acceptable.

2.4. Clinical efficacy and safety

Efficacy and safety data of the paediatric studies for Xydalba were assessed within a previous Type II variation (EMA/H/C/002840/II/0043). This submission includes final study results from Study DUR001-306 which enrolled one additional participant in Cohort 5 (birth to < 3 months) since the aforementioned previous Type II variation submission. This subject had a favourable clinical outcome.

The overall conclusions of Study DUR001-306 and on the safety and efficacy of dalbavancin in paediatric patients remain unchanged and are consistent with the Type II variation previously assessed by the CHMP.

2.4.1. 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.

2.5. Risk management plan

The MAH submitted an updated RMP version 8.0 with this application. This RMP was further updated (version 8.1) in response to the CHMP Request for Supplementary Information during the assessment of this Type II to extend the paediatric indication to the age range of birth to < 3 months.

Updates included the following:

- inclusion of information related to safety concern "Use in pregnant and lactating women" in Table 38 (Part II Module S.VII.3 of RMP) which was inadvertently deleted in the version 8.0.
- amendment of the proposed indication.
- minor editorial changes to align with the changes recommended for the SmPC.

The CHMP endorsed the Risk Management Plan version 8.1 with this procedure.

2.5.1. Safety specifications

Epidemiology of the indications and target population

Module SI was updated to propose extension of indication of Xydalba to the paediatric population (aged birth to < 3 months) for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI), including paediatric patients aged less than 3 months with suspected or confirmed sepsis associated with skin and subcutaneous tissue infections.

Additionally, incidence, prevalence of target population, demographic profile of target population, potential health risks in paediatric patients were updated.

Information about main treatment options, mortality in target indication, sepsis in patients aged less than 3 months was also updated.

The product overview and Module SI were updated to amend the proposed indication of Xydalba for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and paediatric patients from birth.

Finally, the posology and information about renal impairment in paediatric patients were updated in the product overview.

Clinical trial exposure

Brief overview of development

Module SIII was updated to the extent that the use of dalbavancin therapy for the treatment of ABSSSI (and suspected/confirmed sepsis if <3 months old) was also studied in a paediatric population aged birth to <18 years in the DUR001-306 study, with supporting PK/safety data from 3 Phase 1 PK studies (A8841004, DUR001 106, and DALPK02).

Clinical Trial Exposure

Treatment	Number of Subjects
Dalbavancin	3124
Active Comparator	1316
Placebo	72

¹ The 5 patients (3 received Dalbavancin and 2 received Placebo) from VER001-3 study are not included due to dosing schedules that were dramatically different from the proposed dosing schedule.

Age Range (years)	Number of Subjects		
	Male	Female	Total
0 - <6	57	36	93
6 - <18	83	46	129
18 - <65	1508	946	2454
65 - <75	147	116	263
>= 75	63	122	185
Total	1858	1266	3124

¹ The 5 patients (3 received Dalbavancin and 2 received Placebo) from VER001-3 study are not included due to dosing schedules that were dramatically different from the proposed dosing schedule.

Racial Group	Number of Subjects
White	2516
Black or African American	258
Asian	102
American Indian or Alaska Native	18
Native Hawaiian/Other Pacific Islander	3
Other	227
Total	3124

¹ The 5 patients (3 received Dalbavancin and 2 received Placebo) from VER001-3 study are not included due to dosing schedules that were dramatically different from the proposed dosing schedule.

Study number (Phase)	No. of patients exposed to dalbavancin	Age Range
DUR001-306 (Phase 3)	169	Birth-17 years
DAL-PK-02 (Phase 1)	8	<3 months
A8841004 (Phase 1)	10	12-17 years
DUR001-106 (Phase 1)	34	3 months-11 years

The Committee acknowledged that Module SIII was updated with the latest clinical trial exposure numbers (exposure number updated from 3123 to 3124 persons in dalbavancin treatment group). This module was also updated with the clinical trial exposure numbers in paediatric population (total 221 patients). The proposed updates are acceptable.

Populations not studied in clinical trials

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

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 authorisation in Europe.

Ten adolescents aged 12 to 16 years old were enrolled in the PK study A8841004, and 34 subjects aged 3 months to 11 years old were enrolled in study DUR001-106. Eight subjects (neonates to infants <3 months) with suspected or confirmed bacterial infection were enrolled in PK study DAL-PK-02. A total of 199 subjects with ABSSSI from birth to age <18 years old or with suspected/confirmed sepsis if <3 months old were enrolled in Study DUR001-306.

Study DUR001-306 assessed the safety and efficacy of dalbavancin for the treatment of ABSSSI (or suspected/confirmed sepsis if less than 3 months of age) in children, from birth to 17 years (inclusive). Table 27 and Table 28 provide a comparison of frequency of adverse events seen in the Phase 3 study by age groups in dalbavancin and comparator-treated subjects, respectively. Overall, a low proportion of subjects experienced a treatment-emergent adverse event (TEAE) (9.9% 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). Within each of the 4 age cohorts, at least 1 subject experienced a TEAE in each of the dalbavancin treatment arms, with the exception of subjects in the 2-dose dalbavancin arm within the 6 years to <12 years age cohort. In the Birth to <3 months age cohort, the TEAEs occurred in the dalbavancin single-dose group as subjects in this age cohort only received the single-dose treatment. The 1 TEAE in the comparator arm was reported in the 2 years to <6 years age cohort. No treatment-related TEAEs were reported in the study. Three treatment-emergent serious adverse events (TESAEs) were reported, all in the dalbavancin single-dose arm; with 1 each in the Birth to <3 months, 3 months to <2 years, and 12 years to 17 years age cohorts. There were no treatment-related TESAEs, no AEs leading to discontinuation of study intervention or study, and no TESAEs leading to death.

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

	Age Group								
	Age Birth to <3 months	Age 3 months to <2 years		Age 2 years to <6 years		Age 6 years to <12 years		Age 12 years to 17 years	
	Dalbavancin Single-Dose (N=10) n/N (%)	Dalbavancin Single-Dose (N=9) n/N (%)	Dalbavancin Two-Dose (N=8) n/N (%)	Dalbavancin Single-Dose (N=18) n/N (%)	Dalbavancin Two-Dose (N=17) n/N (%)	Dalbavancin Single-Dose (N=25) n/N (%)	Dalbavancin Two-Dose (N=24) n/N (%)	Dalbavancin Single-Dose (N=29) n/N (%)	Dalbavancin Two-Dose (N=29) n/N (%)
Number of Patients Who Experienced at Least One:									
AE	3/10 (30.0)	3/9 (33.3)	4/8 (50.0)	1/18 (5.6)	1/17 (5.9)	1/25 (4.0)	1/24 (4.2)	1/29 (3.4)	2/29 (6.9)
Treatment-emergent AE (TEAE)	3/10 (30.0)	3/9 (33.3)	4/8 (50.0)	1/18 (5.6)	1/17 (5.9)	1/25 (4.0)	0	1/29 (3.4)	2/29 (6.9)
Treatment-related TEAE	0	0	0	0	0	0	0	0	0
Treatment-emergent Serious AE (TESAE)	1/10 (10.0)	1/9 (11.1)	0	0	0	0	0	1/29 (3.4)	0
Treatment-related TESAE	0	0	0	0	0	0	0	0	0
AE leading to study treatment discontinuation	0	0	0	0	0	0	0	0	0
AE leading to study discontinuation	0	0	0	0	0	0	0	0	0
TESAE leading to death	0	0	0	0	0	0	0	0	0

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

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

Table 29 provides the most common reported TEAEs overall ($\geq 2\%$ of subjects in any treatment group regardless of age group) for each of the different age groups. Only two age groups experienced common TEAEs. Overall, common TEAEs that occurred in more than 1 subject in any treatment arm were pyrexia and cough (each in 2 subjects in the dalbavancin two-dose arm). The remaining most common TEAEs, nasopharyngitis and postoperative anaemia, occurred in no more than 1 subject in any treatment arm.

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

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

The CHMP acknowledged that Module SIV was updated with the frequency of adverse events seen in the study DUR001-306, which is endorsed.

Post-authorisation experience

Exposure

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

Cumulatively, through to 22 November 2023, the total number of dalbavancin vials distributed was 1,319,278 vials which equates to 439,759 patients.

There have been 976,670 vials distributed in the US, 300,015 vials distributed in the EU, and 42,593 vials distributed in rest of world. Exposure by age and gender are provided in Table 5.

Table 5 Cumulative exposure to dalbavancin

	<i>Sex^a</i>		<i>Age^a</i>			<i>Region^c</i>		
	<i>M</i>	<i>F</i>	<i>0-17</i>	<i>18-64</i>	<i>>65</i>	<i>USA</i>	<i>EEA</i>	<i>ROW</i>
Cumulative exposure								
Vials sold	649,486	327,184	0	732,503	244,168	976,670	300,015	42,593
Estimated exposure ^b	216,495	109,061	0	244,168	81,389	325,557	100,005	14,198

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

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

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

The CHMP acknowledged that Module SV was updated with the latest estimated post-authorisation exposure numbers (cumulative estimates calculated to 22 November 2023). Based on these sales data,

an estimated 1,319,278 vials were distributed cumulatively, which the MAH has equated to be 439,759 patients exposed. The proposed updates are acceptable.

Identified and potential risks

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

Important Identified Risk

Emergence of resistance

Cumulatively until the DLP (17-Jan-2024), there have been 185 cases in the global safety database which met search criteria for the important identified risk emergence of resistance and they reported 193 relevant events (61 serious and 132 nonserious). The outcomes of these events were unknown (139), resolved/ resolving (47), Ongoing (4), fatal (2), NA (1). The fatal cases reported skin bacterial infection and drug ineffective, respectively, with insufficient information for further assessment regarding the patient's full medical history, diagnostic tests with results, cause of death, autopsy report, and concomitant medications. To date, none of these cases were indicative of emergence of resistance (due to either absence of culture or sensitivity information or absence of bacterial isolate information in cases where dalbavancin was used for an unapproved indication).

Pseudomembranous colitis

Cumulatively until the DLP, there have been 9 cases in the global safety database reporting Pseudomembranous colitis. Of these 9 cases, 5 cases reported serious events and 4 cases reported nonserious events of *Clostridioides difficile* colitis/ *Clostridioides difficile* infection. The outcome of the events was resolved (4), unknown (3), ongoing and fatal (1 each). The fatal case reported *C. difficile* colitis in a patient with medical history of recurrent *C. difficile* colitis prior to dalbavancin (ongoing with start date approximately 11 months before dalbavancin therapy initiation). However, the cause of death was not provided and no autopsy was performed. These reports are consistent with the known characterisation of this risk.

Hypersensitivity

Cumulatively until the DLP, there have been 352 cases in the global safety database meeting the search criteria for Hypersensitivity. The 352 cases reported 446 relevant events (157 serious and 289 nonserious), of which the most commonly reported events were rash, urticaria and hypersensitivity. Overall, the outcome of relevant events was resolved/ resolving (276), unknown (139), ongoing (31). These reports are consistent with the established characterization of the safety concern.

Important Potential Risk

Hepatic disorders

Cumulatively until the DLP, there have been 25 cases in the global safety database that met the criteria for this risk. The 25 cases reported 29 relevant events (20 serious and 9 nonserious). The outcome of these events was resolved/ resolving (19), unknown (7), ongoing (2), fatal (1). The fatal case reported hepatic cholestatic before dalbavancin start date, and there is insufficient information for a proper assessment regarding the patient's full medical history, cause of death, autopsy report, event details and treatment received. The remaining reports are consistent with the established characterization of the safety concern.

Otovestibular toxicity

Cumulatively until the DLP, there have been 5 cases in the global safety database that met the criteria for this risk. The 5 cases reported 7 relevant events (2 serious and 5 nonserious). The outcome of events was unknown (4), ongoing (2) and resolved (1). These reports are consistent with the established characterization of the safety concern.

Nephrotoxicity

Cumulatively until the DLP, there have been 58 cases in the global safety database that met the criteria for this risk. The 58 cases reported 65 relevant events (51 serious and 14 nonserious). The outcome of these events was reported as unknown (29), resolved/ resolving (24), ongoing (11) and fatal (1). The fatal case reported renal failure due to non-alcoholic steatohepatitis in a patient with medical history of cirrhosis. The remaining reports are consistent with the established characterization of the safety concern.

Haematologic Effects

Cumulatively until the DLP, there have been 59 cases in the global safety database that met the criteria for this risk. The 59 cases reported 64 relevant events (47 serious and 17 nonserious). The outcome of events was reported as resolved/resolving (30), ongoing (17), unknown (16) and fatal (1). The fatal case reported anaemia in patient with medical history of Sweet's syndrome and Myelodysplastic syndrome. The remaining reports are consistent with the established characterization of the safety concern.

The Committee acknowledged that Module SVII was updated with the latest data from post-marketing experience. The MAH also updated subsection "Missing information" by removing information related to safety concern "Paediatric use" from Table 38 (Part II Module S.VII.3 of RMP), which is acceptable.

2.5.2. 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 • Use in pregnant and lactating women

The Committee acknowledged that the MAH updated subsection "Missing information" by removing the safety concern "Paediatric use" from the Table 39 (Part II Module S.VIII. of RMP). Considering that full age range of paediatric population would be covered in indications of dalabavancin after approval of this

type II variation, the proposed update was acceptable. No further changes had been made in the Summary of safety specification.

2.5.3. Pharmacovigilance plan

Routine Pharmacovigilance Activities

Emergence of resistance		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities including targeted follow up- questionnaire for lack of efficacy	To assure continuous monitoring of adverse events of potential resistance to dalbavancin, such as cases reported as lack of efficacy.

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

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

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

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

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

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

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

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

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

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

The Committee acknowledged that Study 'In vitro surveillance to monitor any changes in susceptibility of key label pathogens for five years post approval in the US as part of a PMR' was removed from the routine pharmacovigilance activities.

Paediatric use is no longer in Safety concerns, therefore studies in paediatric use were removed from the routine pharmacovigilance activities, which is acceptable.

Additional pharmacovigilance activities

There are no current additional pharmacovigilance activities and the Committee acknowledged that no new studies/activities were completed during the period.

Routine Risk Minimisation Measures by Safety Concern

The MAH proposed the following changes to the SmPC:

Nephrotoxicity

The MAH proposed wording for recommended dosage adjustments in patients with renal impairment in SmPC sections 4.2 and 5.1.

Section 4.2:

Paediatric patients

The recommended dosage regimen of dalbavancin in paediatric patients is a single dose regimen based on the age and weight of the patient (Table below). Administer dalbavancin over 30 minutes by intravenous infusion.

Dosage of Xydalba in Paediatric Patients with Creatinine Clearance* of 30 mL/min/1.73m² or Higher

Age Range	Dosage (Single Dose Regimen)
Birth to less than 6 years	22.5 mg/kg (maximum 1 500 mg)
6 to less than 18 years	18 mg/kg (maximum 1 500 mg)

Section 5.1:

Xydalba has been evaluated in paediatric patients aged from birth to < 18 years with ABSSSI (or suspected or confirmed sepsis if aged less than 3 months old) in one Phase 3 open-label, randomised, comparator controlled clinical trial. The study included 169 patients treated with dalbavancin (91 patients treated with a single dose of dalbavancin and 78 patients, all of them aged 3 months and older, treated with a two-dose regimen of dalbavancin) and 30 patients treated with comparator. Seven of 10 patients aged less than 3 months were enrolled with suspected or confirmed sepsis. The primary objective was to assess the safety and tolerability of dalbavancin and secondary objectives included assessment of efficacy and pharmacokinetics. Efficacy was a descriptive endpoint. Clinical cure rate at TOC (mITT) was 95.2 % (79/83) in the dalbavancin single-dose arm, 97.3 % (72/74) in the dalbavancin two-dose arm, and 100 % (30/30) in the comparator arm.

Safety issues related to paediatric use of Xydalba are adequately addressed in the SmPC. This was endorsed by the Committee.

2.5.4. Overall conclusion on the RMP

The changes to the RMP were considered and Risk Management Plan version 8.1 is approved with this procedure.

2.6. 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 and 6.6 of the SmPC have been updated. The Package Leaflet is updated accordingly.

During the assessment, the MAH was asked to resolve minor issues in Sections 4.2, 4.4 and 5.2 related to renal impairment in children <3 months for the SmPC could be considered acceptable. The issues were resolved by provision of product information documents amended according to the recommendations of the CHMP.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed by QRD and accepted by the CHMP, including the replacement of the MIC breakpoints table in section 5.1 of the SmPC with the agreed reference to the EMA website.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Luxembourg, Denmark, the Netherlands, Norway, Iceland, Finland and Sweden.

2.6.1. 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 the initial MAA for 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

Acute bacterial skin and skin structure infection (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 was a multicentre, open-label, randomised, comparator-controlled trial of the safety and efficacy of dalbavancin versus active comparator in paediatric subjects with ABSSSI including 199 participants. This 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 with an age from birth to < 3 years of age.

This study compared a 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 the criteria for oral therapy. Children in Cohort 5 were not included in the randomisation scheme and were all assigned to single-dose dalbavancin.

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 dalbavancin plasma exposures in children to those in adults. The acceptance of extrapolation is based on assumptions that the disease (including pathogen), mechanism of action and thus PK/PD are the same in paediatric patients as in adults. Therefore, the selected doses should achieve comparable plasma exposure and probability of PK/PD target attainment (PTA) between children and adults.

3.2. Favourable effects

The paediatric clinical database used in the pharmacokinetic analysis included a total of 3 pre-term patients, 5 term patients and 10 patients between 28 days to < 3 months. The paediatric PK exposures

were generally comparable between children and adults. However, the exposure was slightly lower in preterm neonates, albeit still within the adult target exposure range, which is acceptable. In addition, there were PTA analyses which supported satisfactory response in all age groups (including preterm neonates).

Efficacy data of the paediatric studies for Xydalba including subjects from birth to <3 months of age were assessed within the previous Type II variation (EMA/H/C/002840/II/0043). The current submission includes final study results from Study DUR001-306 which enrolled one additional participant in Cohort 5 (birth to < 3 months) since the previous Type II variation submission. This subject had a favourable clinical outcome.

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, which is however acceptable as the application relies on the concept of extrapolation of clinical efficacy and safety based on comparable dalbavancin plasma exposures in children to those in adults.

3.4. Unfavourable effects

Overall, a low proportion of subjects experienced a treatment-emergent adverse event: 9.9% 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.

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. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

This extension of indications application to include the paediatric population (from birth to < 3 months) for the treatment of ABSSSI relies on the concept of extrapolation of clinical efficacy and safety based on comparable plasma exposures in children to those in adults.

The proposed dose is a single dose of 22.5 mg/kg (maximum 1 500 mg). The MAH did not propose to include the alternative two-dose regimen for the paediatric population in the SmPC, which is acceptable as there is no added benefit of having the option of using a two-dose regimen.

The proposed dose can be considered satisfactory for all age groups based on comparisons of PK exposures and probability of target attainment (PTA) analyses.

Efficacy and safety data of the paediatric studies for Xydalba were already assessed within a previous Type II variation (EMA/H/C/002840/II/0043). The submission dossier included final study results from Study DUR001-306, which enrolled one additional participant having a favourable clinical outcome.

It should be noted that the entire paediatric clinical database (used in the pharmacokinetic analysis) included a total of 3 pre-term patients, 5 term patients and 10 patients between 28 days to < 3 months.

The overall conclusions on the safety and efficacy of dalbavancin in paediatric patients remain unchanged and consistent with the aforementioned Type II variation previously assessed by the CHMP.

3.6.2. Balance of benefits and risks

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

3.7. Conclusions

The overall benefit-risk of Xydalba for the proposed indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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, IIIA and IIIB

Extension of indication to include the treatment of acute bacterial skin and skin structure infections (ABSSSI) in paediatric patients from birth for Xydalba, based on final results from study DUR001-306, together with data from three Phase 1 PK studies (A8841004, DUR001-106, and DUR001-107 (DAL-PK-02); DUR001-306 was a Phase 3, multicenter, open-label, randomised, 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. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP is approved with this variation. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI, update the list of local representatives in the Package Leaflet in line with the latest QRD template version 10.4, and replace the MIC breakpoints table in section 5.1 of the SmPC with the agreed reference to the EMA website, in line with EMA's Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA 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 P/0467/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Xydalba- EMEA/H/C/002840/II/0050'