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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xydalba

dalbavancin

Procedure no: EMEA/H/C/002840/P46/003

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 28th April 2020, the MAH submitted a completed paediatric study for Study 6 [A8841014 (DUR001-107)] of the Xydalba (EMEA/H/C/002840) paediatric investigation plan (PIP), in accordance with Article 46 of Regulation (EC) No 1901/2006. A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that PIP Study 6 [A8841014 (DUR001-107), the global code is DAL-PK-02] is part of the ongoing PIP development program (completion date of PIP study 7 is expected to be December 2021). The termination of PIP study 6 was agreed in the latest PIP modification, EMEA-000016-PIP01-07-M07.

It is noted that a variation application consisting of the full relevant data package (i.e. containing several studies including PIP study 6) is expected to be submitted by December 2022.

2.2. Information on the pharmaceutical formulation used in the study

Details on the formulation characteristics of dalbavancin are as follows:

• Name of Finished Product: Xydalba 500 mg powder for concentrate for solution for infusion

• Name Active Ingredient: dalbavancin

• Name of Inactive Ingredients: mannitol (129 mg); lactose (129 mg); hydrochloric acid and/or sodium hydroxide for pH adjustment 4.0 to 5.0

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for PIP Study 6 [A8841014 (DUR001-107), the global code is DAL-PK-02]; Pharmacokinetics of a Single-dose of Dalbavancin in Preterm Neonates to Infants Ages < 3 Months with Suspected or Confirmed Bacterial Infection.

2.3.2. Clinical study

PIP Study 6 [A8841014 (DUR001-107), the global code is DAL-PK-02]

Description

Determination of pharmacokinetics of dalbavancin in paediatric patients with suspected or confirmed bacterial infections aged less than 3 months for selection for dosing for a phase 3 study in children with late-onset sepsis.

Methods

Objectives

Primary objective

- To evaluate the pharmacokinetic (PK) profile of a single intravenous infusion (IV) infusion dose of dalbavancin. The primary endpoint was the plasma concentration of dalbavancin.

Secondary objective

- PK parameters, including: maximum plasma drug concentration (C_{max}), time of C_{max} (T_{max}), area under the plasma concentration versus time curve from time 0 to t and 0 to infinity (AUC_{0-t} and AUC_{0-inf}), clearance (CL), volume of distribution at steady-state (V_{ss}) and terminal elimination half-life ($t_{1/2}$).
- To evaluate the safety and tolerability of a single dalbavancin IV infusion. Safety assessments included adverse events (AE), audiology testing, clinical laboratory values, vital signs (including weight and temperature) and physical examination findings.

Study design

This study was a multiple-centre, randomised, open-label, single-dose study in paediatric participants with known or suspected bacterial infection. No more than 20% of these evaluable participants were to have urinary tract infections due to Gram-positive organisms. Participants received a single intravenous infusion dose of 22.5 mg/kg over 30 minutes on Day 1.

Study population /Sample size

A total of 22 participants were planned in three cohorts: 6 participants in Cohort 1, and 8 participants each in Cohorts 2 and 3. Eight participants were enrolled (6 in Cohort 1 and 1 each in Cohorts 2 and 3) and included in both the PK and Safety analysis populations.

- 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

Main criteria for eligibility
Male and female participants who are preterm neonates (gestational age ≥ 32 to < 37 weeks, aged ≤ 28 days), term neonates (gestational age ≥ 37 weeks, aged ≤ 28 days) or young infants (aged 28 days to < 3 months) who were receiving at least 24 hours of appropriate non-investigational intravenous anti-infective treatment other than glycopeptide antibiotics for known or suspected bacterial infections.

Treatments

All participants in each cohort were administered a single IV dose of 22.5 mg/kg dalbavancin only (Xydalba 500 mg powder for concentrate for solution for infusion), in a 30 minute (± 5 minutes) (including flushing to ensure that all of the investigational product [IP] has been administered) on Day 1 via peripheral or central infusion line; this treatment with IP was to be in addition to background anti-infective treatment to be chosen by the investigator according to standard of care, except for the excluded medications vancomycin or other glycopeptide antibiotics. Dalbavancin was provided in single-use 50 mL vials containing 500 mg of dalbavancin. Each vial was reconstituted and further diluted prior to administration by addition of 5% dextrose (5% glucose) solution (D5W) in accordance with the Study Manual.

Outcomes/endpoints

Pharmacokinetics
Appropriate PK parameters were computed for dalbavancin using a model independent (non-compartmental) approach with the software Pharsight Phoenix WinNonlin (version 8.0). Plasma concentration data for dalbavancin from this study will also be pooled with data from other studies in a population PK analysis that will be reported separately. PK parameters computed for dalbavancin using population PK analysis are not included in this clinical study report (CSR).

Safety
Safety measures included evaluation of AEs, audiology, clinical laboratory evaluations, vital signs (systolic and diastolic blood pressure (BP), pulse rate, body weight, respiration rate, and temperature), and physical examinations (abnormal findings were to be reported as AEs).

Statistical Methods

- The safety population consisted of all participants who received the dose of the investigational product. All demographic and safety summaries were conducted using the safety population.
- The PK analysis population consisted of all participants who received the dose of IP and have at least one measurable plasma concentration.

Pharmacokinetics
Descriptive statistics (arithmetic mean, standard deviation, maximum, median, minimum, geometric mean, geometric mean CV%) were reported for plasma dalbavancin concentration data at all time-points by Cohort and overall and were calculated for all PK parameters by Cohort using the PK population.

Safety
Safety parameters, including AEs (including abnormal findings on physical examination), clinical laboratory parameters, and vital sign parameters, were summarised using descriptive statistics (number and percentage of participants for categorical variables and mean, standard deviation, median, minimum, and maximum values for continuous variables). Audiology findings were summarised by cohort and in total for the Safety population using shift analyses and categorical and continuous descriptive statistics. All patients must have an audiologic assessment performed prior to dalbavancin dosing and at Day 28. If the event of abnormalities found at day 28 audiological testing must be repeated at the final study visit (3- and 6-months post dose or until they return to baseline).

Results

Recruitment/ Number analysed

Participant Disposition and Demographics
A total of 8 participants were enrolled in the study and received investigational product: 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). All 8 (100%) participants completed the study as planned and no participant prematurely discontinued from the study. The mean age was 40.6 days (range: 6 to 65 days) across all 3 Cohorts with a gestational age of 36.1 weeks (range: 28 to 41 weeks). Six participants were female and 2 were male. Seven participants were white, and 1 participant was of multiple race. Overall participant weight (SD) and height (SD) was 3.49 (0.772) kg (range: 2.6 to 4.5 kg) and 51.06 (4.460) cm (range: 44.5 to 57.0 cm), respectively, with an overall BMI (SD) of 13.24 (1.371) kg/m^2 (range: 11.2 to 14.6 kg/m^2)

Pharmacokinetic results

The safety and PK of dalbavancin have previously been established in adults at doses of up to 1500 mg. Furthermore, the safety and PK of dalbavancin in paediatric population have been previously evaluated in children aged ≥ 3 months.

For the present PK study (children aged <3 months), the dalbavancin dose was chosen based on the experience observed in children aged ≥ 3 months in Study DUR001-106 and Study A8841004, and the predicted exposure from a population PK model. The predicted exposure at a dose of 22.5 mg/kg was similar to that at a dose of 1500 mg in adults.

All study participants of the present PK study have received a single intravenous infusion dose of 22.5 mg/kg over 30 minutes on Day 1. Blood samples for the determination of plasma concentrations of dalbavancin were collected at the following times from all 8 participants:

• Day 1: at the end of infusion (including the flushing) (+ 5 min)

• Day 1: between 2 to 6 hours after start of infusion

• Day 1: between 10 to 14 hours after start of infusion

• Day 2: between 20 to 28 hours after start of infusion on Day 1

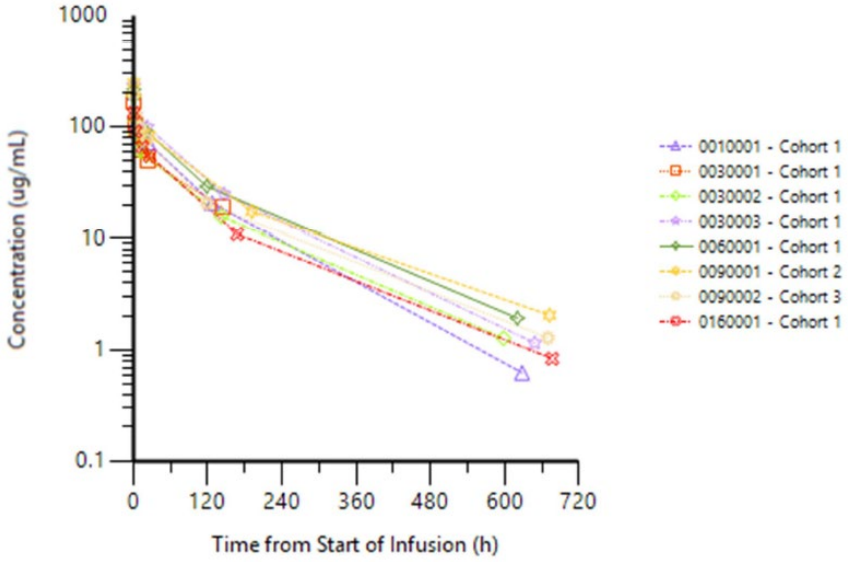
• Day 7: between 96 to 192 hours (Days 5 to 9) after start of infusion on Day 1

• Day 28: between 552 to 744 hours (Days 24 to 32) after start of infusion on Day 1

Following a single dose of 22.5 mg/kg dalbavancin as a 30-minute IV infusion, T_{max} occurred around the time of the end of the infusion, i.e. around 0.5 h. The mean (SD) C_{max} for Cohort 1 (n = 6) was 191.58 (39.96) µg/mL, and the C_{max} values for the single participants enrolled in Cohorts 2 and 3 were 250.85 and 198.66 µg/mL, respectively. $t_{1/2}$ values for the single participants in Cohorts 2 and 3 were 122.89 and 111.20 h, respectively, and were similar to the mean value for Cohort 1 (103.26 [9.14] h). The mean concentration for the Day 28 PK sample across cohorts was 0.973 (0.655) µg/mL, and 7 of 8 participants had plasma concentrations exceeding 0.5 µg/mL at this time point.

Mean CL for Cohort 1 was 7.74 (SD of 1.85) mL/h, and the CL values for the participants enrolled in Cohorts 2 and 3 were 5.04 and 5.77 mL/h, respectively. Mean AUC parameters (AUC_{0-t}, AUC_{0-120}, AUC_{0-inf}) for Cohort 1 were similar to the observed values in the single participants in Cohorts 2 and 3. The mean value of AUC_{0-120} was 6247.89 (1493.99) h*µg/mL for Cohort 1, 7758.40 h*µg/mL for the participant in Cohort 2, and 6512.44 h*µg/mL for the participant in Cohort 3.

Figure 1. Plasma Concentrations of Dalbavancin Versus Time Following Administration of 22.5 mg/kg Dalbavancin as a 30-Minute IV Infusion to Paediatric Participants from Birth to < 3 months Years in Cohorts 1, 2, and 3 – Semi-Logarithmic Scale.



Overview of individual and mean PK parameter values obtained for the Cohort 1 (n=6) is given in the table below.

Table 1. Individual and Mean Dalbavancin PK Parameters Following Single Dose Administration of 22.5 mg/kg Dalbavancin as a 30-minute Infusion to Paediatric Participants from > 28 days to < 3 Months in Cohort 1.

SUBJID	T_{max} (h)	C_{max} (µg/mL)	λ_z (1/h)	$T_{1/2}$ (h)	AUC_{0-t} (h*ug/mL)	AUC_{0-120} (h*ug/mL)	AUC_{0-inf} (h*ug/mL)	AUC% (%)	CL (mL/h)	V_{ss} (mL)
0010001	0.57	203.74	0.008	89.15	9355.07	6315.95	9435.58	0.85	10.74	1244.31
0030001*	0.62	166.45	0.009	79.96	5595.93	5064.72	7758.84	27.88	11.60	1301.67
0030002	0.60	191.10	0.006	107.19	8007.50	4988.12	8205.14	2.41	7.96	1134.38
0030003	0.60	236.60	0.007	99.40	13218.66	8541.66	13385.01	1.24	6.90	898.24
0060001	0.58	217.79	0.006	111.98	12509.97	7493.41	12822.89	2.44	5.79	876.84
0160001	0.67	133.82	0.006	108.60	7786.76	5083.49	7918.21	1.66	7.32	1002.69
N	**6**	**6**	**5**	**5**	**6**	**6**	**5**	**6**	**5**	**5**
Mean	**0.607**	**191.581**	**0.007**	**103.263**	**9412.315**	**6247.891**	**10353.366**	**6.080**	**7.742**	**1031.292**
SD	**0.036**	**36.960**	**0.001**	**9.139**	**2941.691**	**1493.993**	**2582.469**	**10.696**	**1.850**	**156.828**
Min	**0.57**	**133.82**	**0.01**	**89.15**	**5595.93**	**4988.12**	**7918.21**	**0.85**	**5.79**	**876.84**
Median	**0.60**	**197.42**	**0.01**	**107.19**	**8681.28**	**5699.72**	**9435.58**	**2.03**	**7.32**	**1002.69**
Max	**0.67**	**236.60**	**0.01**	**111.98**	**13218.66**	**8541.66**	**13385.01**	**27.88**	**10.74**	**1244.31**
CV%	**5.9**	**19.3**	**9.4**	**8.9**	**31.3**	**23.9**	**24.9**	**175.9**	**23.9**	**15.2**
Geometric Mean	**0.606**	**188.377**	**0.007**	**102.925**	**9023.385**	**6107.813**	**10102.230**	**2.570**	**7.579**	**1021.958**
CV% Geometric Mean	**5.74**	**20.79**	**9.17**	**9.17**	**33.04**	**23.34**	**25.04**	**189.59**	**22.98**	**15.09**

* λ_z, $T_{1/2}$, AUC_{0-inf}, CL, and V_{ss} values for participant 003001 were not included in descriptive statistics because AUC% was > 20%

Overview of individual PK parameter values obtained for Cohort 2 (n=1) and Cohort 3 (n=1) is given in the table below.

Table 2. Individual Dalbavancin PK Parameters Following Single Dose Administration of 22.5 mg/kg Dalbavancin as a 30-minute Infusion to Paediatric Participants from Birth to 28 Days in Cohort 2 and 3.

SUBJID	COHORT	T_{max} (h)	C_{max} (µg/mL)	λ_z (1/h)	$T_{1/2}$ (h)	AUC_{0-t} (h*ug/mL)	AUC_{0-120} (h*ug/mL)	AUC_{0-inf} (h*ug/mL)	AUC% (%)	CL (mL/h)	V_{ss} (mL)
0090001	2	0.58	250.85	0.006	122.89	13016.77	7758.40	13380.93	2.72	5.04	819.34
0090002	3	0.57	198.66	0.006	111.20	10329.65	6512.44	10536.28	1.96	5.77	831.52

According to the MAH, while the average clearance of dalbavancin Cohort 1 (participants aged > 28 days to < 3 months) was greater than the typical value of CL in adult patients, and AUC_{0-120} was lower in all cohorts than in adults receiving 1500 mg, drug exposures were still within the range where efficacy would be predicted based on nonclinical models. Furthermore, MAH stated that the PK data from this study will be combined with additional data from clinical studies of dalbavancin in paediatric patients (Studies A8841004, DUR001-106, DUR001-306) in a population PK analysis (to be reported separately). The updated population PK model will then be used to conduct PK/PD target attainment simulations to support dosing of dalbavancin in paediatric patients from birth to < 18 years.

Efficacy results

Not applicable.

Safety results

Adverse events

A total of 8 participants received dalbavancin 22.5 mg/kg (single IV infusion over 30 minutes) as per protocol in this study.

Table 3. Overall Summary of Adverse Events (Safety Population)

Category of Adverse Event, n (%)	Cohort 1 (n = 6)	Cohort 2 (n = 1)	Cohort 3 (n = 1)	Total (N = 8)
Treatment-emergent adverse events (TEAE)	6 (100.0)	0	0	6 (75.0)
Deaths	0	0	0	0
Treatment-emergent serious adverse events (TESAE)	1 (16.7)	0	0	1 (12.5)
TEAE Leading to Treatment Discontinuation	0	0	0	0

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

A majority of the treatment-emergent adverse events (TEAEs) were mild or moderate in severity. The most commonly reported TEAEs were pyrexia (3 [37.5%] participants) and procedural pain (2 [25.0%] participants); all in Cohort 1. All other TEAEs in all cohorts were reported as single instances. In total, 36 AEs were reported during the study; 35/36 were TEAEs. In 19/35, the event recovered/resolved during the study, and in 8/35 was recovering/resolving. For the remaining 8/35, the events were not recovered at the time of last report.

Table 4. Participants with Treatment-Emergent Adverse Events (TEAE), System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term, n (%)	Cohort 1 (n = 6)	Cohort 2 (n = 1)	Cohort 3 (n = 1)	Total (N = 8)
Participants with at least one TEAE	**6 (100.0)**	**0**	**0**	**6 (75.0)**
Cardiac disorders	3 (50.0)	0	0	3 (37.5)
Atrial thrombosis	1 (16.7)	0	0	1 (12.5)
Bradycardia	1 (16.7)	0	0	1 (12.5)
Left ventricular dysfunction	1 (16.7)	0	0	1 (12.5)
Tachycardia	1 (16.7)	0	0	1 (12.5)
Gastrointestinal disorders	3 (50.0)	0	0	3 (37.5)
Abdominal pain	1 (16.7)	0	0	1 (12.5)
Constipation	1 (16.7)	0	0	1 (12.5)
Flatulence	1 (16.7)	0	0	1 (12.5)
Gastrooesophageal reflux disease	1 (16.7)	0	0	1 (12.5)
Necrotising colitis	1 (16.7)	0	0	1 (12.5)
Vomiting	1 (16.7)	0	0	1 (12.5)
General disorders and administration site conditions	3 (50.0)	0	0	3 (37.5)
Pyrexia	3 (50.0)	0	0	3 (37.5)
Hypothermia	1 (16.7)	0	0	1 (12.5)
Withdrawal syndrome	1 (16.7)	0	0	1 (12.5)
Infections and infestations	3 (50.0)	0	0	3 (37.5)
Bacterial tracheitis	1 (16.7)	0	0	1 (12.5)
Oral hairy leukoplakia	1 (16.7)	0	0	1 (12.5)
Stoma site cellulitis	1 (16.7)	0	0	1 (12.5)
Injury, poisoning and procedural complications	2 (33.3)	0	0	2 (25.0)
Procedural pain	2 (33.3)	0	0	2 (25.0)
Investigations	3 (50.0)	0	0	3 (37.5)
Blood alkaline phosphatase increased	1 (16.7)	0	0	1 (12.5)
Fungal test positive	1 (16.7)	0	0	1 (12.5)
Liver function test increased	1 (16.7)	0	0	1 (12.5)
Metabolism and nutrition disorders	2 (33.3)	0	0	2 (25.0)
Feeding intolerance	1 (16.7)	0	0	1 (12.5)
Hypovolaemia	1 (16.7)	0	0	1 (12.5)
Nervous system disorders	1 (16.7)	0	0	1 (12.5)
Hydrocephalus	1 (16.7)	0	0	1 (12.5)
Paroxysmal sympathetic hyperactivity	1 (16.7)	0	0	1 (12.5)
Seizure	1 (16.7)	0	0	1 (12.5)
Psychiatric disorders	1 (16.7)	0	0	1 (12.5)
Irritability	1 (16.7)	0	0	1 (12.5)
Respiratory, thoracic and mediastinal disorders	2 (33.3)	0	0	2 (25.0)
Apnoea	1 (16.7)	0	0	1 (12.5)
Pleural effusion	1 (16.7)	0	0	1 (12.5)
Skin and subcutaneous tissue disorders	2 (33.3)	0	0	2 (25.0)
Dermatitis diaper	1 (16.7)	0	0	1 (12.5)
Rash	1 (16.7)	0	0	1 (12.5)
Vascular disorders	1 (16.7)	0	0	1 (12.5)
Brachiocephalic vein thrombosis	1 (16.7)	0	0	1 (12.5)

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

Treatment related adverse events

A total of 3 (37.5%) participants reported non-serious treatment related TEAEs during the study; all in Cohort 1 (vomiting [n=1], oral hairy leucoplakia [n=1] and liver function test increased [n=1]):

-A 30-day-old female (Cohort 1), experienced non-serious TEAE vomiting of moderate severity on Day 1 (04 Nov 2016). The event resolved without sequelae on Day 2(05 Nov 2016). The event was assessed as treatment-related by the investigator.

-A 35-day-old female (Cohort 1), experienced non-serious TEAE oral hairy leucoplakia of mild severity on Day 27 (12 Jun 2018). The event resolved without sequelae on Day 41 (26 Jun 2018). The event was assessed as treatment-related by the investigator.

-A 44-day-old male (Cohort 1), experienced increased liver function test on Day 7 (27 Mar 2017). This TEAE is further described below at the section of laboratory results.

Deaths and serious adverse events

No deaths or discontinuations due to AEs were reported during the study.

One participant (Cohort 1), a 9-week-old male born prematurely (gestational age of 29 weeks), experienced TESAEs (necrotising colitis and hydrocephalus). He received a single intravenous infusion of dalbavancin 65.3 mg over 30 minutes on Day 1 (20 Jan 2017) of the study. The participant had a history of critical illness (since 09 Jan 2017), and severe Group B Strep meningitis/ventriculitis (since 13 Jan 2017), and ventriculomegaly (since 19 Jan 2017). He also had abnormal abdominal X-rays on 16-17 Jan 2017 (details not provided), and a history of pneumatosis intestinalis on abdominal ultrasound (date not provided). Relevant concomitant medications included ampicillin and gentamicin. On Day 4 (23 Jan 2017), a chest X-ray performed to verify placement of a peripherally inserted central catheter showed portal venous gas as an incidental finding. A subsequent abdominal X-ray indicated pneumatosis intestinalis consistent with necrotising enterocolitis (reported as an TESAE of severe necrotising enterocolitis); these findings were assessed as not warranting surgical intervention. He was treated with metronidazole in addition to ampicillin and gentamicin. On Day 5 (24 Jan 2017), repeat X-rays showed improvement. On Day 10 (29 Jan 2017), a repeat MRI scan showed worsening ventriculomegaly. On the same day, an extra-ventricular drain was placed without complication and the low opening pressure suggested ex vacuo hydrocephalus (reported as an TESAE of severe hydrocephalus) secondary to the participant's severe meningitis/ventriculitis. On Day 12 (31 Jan 2017), feedings were restarted with no further issues related to the necrotising enterocolitis. On this date, the TESAE of necrotising enterocolitis resolved. This TESAE was deemed unrelated to IP as the participant had a history of pneumatosis intestinalis on abdominal ultrasound prior to IP administration. On Day 18 (06 Feb 2017), treatment with metronidazole was stopped. The TESAE of hydrocephalus was ongoing at the time of final report. This TESAE was assessed by the investigator as unrelated to IP as the participant had a history of ventriculomegaly and severe meningitis/ventriculitis.

Laboratory results

The following two subjects were reported with postbaseline potentially clinically significant (PCS) clinical laboratory values

One participant (Cohort 1) experienced a PCS high result for platelet count (thrombocytes) (> 2 ×ULN and increase from baseline > 100%) during the interim study period. On Day -2 (screening; 18 Jan 2017) he had a low platelet count of 64 × 109/L (Normal: 150 to 400). On Day 7 his platelet count had increased to 830 × 109/L before returning to normal on Day 26 with a count of 253 × 109/L. The participant also experienced a PCS low for RBC (< 0.8 × LLN and decrease from baseline > 20%) during the interim study period of 2.94 × 1012/L (Normal: 3.80 to 5.50) on Day 7. Low potassium value was also reported (< 0.8 × LLN and decrease from baseline > 15%) of 2.9 mmol/L (Normal: 4.0 to 5.5) on Day 7. His potassium was below the LLN on Day 1 at 3.9 mmol/L before returning to normal

(4.4 mmol/L) at the EOS on Day 26. The abnormal platelet count, RBC and potassium values reported on 26 Jan 2017, were not reported as TEAEs.

One participant (Cohort 1) experienced a PCS high result for ALT (>3.0 × ULN and increase from baseline > 300%) and direct bilirubin (>2.5 × ULN and increase from baseline > 150%) during the interim study period. The subject was a 7-week-old boy (full-term), with a medical history of pulmonary atresia with intact ventricular septum, ductal stent, opioid withdrawal, necrotising enterocolitis, stent occlusion, iliofemoral thrombosis and respiratory failure/mechanical ventilation. The patient was also on long-term total parenteral nutrition (TPN). Prior to dosing (20 Mar 2017 [Study Day –1]), the patient had an elevated conjugated bilirubin and alkaline phosphatase (ALP) as well as a mildly elevated ALT. On Day 7, ALT had increased further to 219 U/L, reaching a maximum value of 252 U/L on Day 10, before returning to normal (28 U/L) on Day 28. His direct bilirubin at screening on Day -1 was elevated at 17.10 µmol/L (Normal 1.71 to 10.26). On Day 7 direct bilirubin had increased further to 39.34 µmol/L, reaching a maximum value of 53.02 µmol/L on Day 10, before returning to normal (3.42 µmol/L) on Day 28. The elevations of bilirubin and liver transaminases were reported as adverse event on Day 7; liver function test increased of mild severity and assessed as related to study treatment by the investigator. This was captured as a non-serious, mild adverse event of liver function test (LFT) increased. The LFT elevations were transient and without constellation of signs/symptoms suggesting liver impairment. No specific examinations were required, nor were therapeutic measures taken in response. There was an episode of fever requiring initiation of antibiotic therapy that started the day prior to the liver enzyme elevation, and hypovolaemia occurring on the day after (albumin human 5% in 20 mL was given on this day). The patient recovered, and his liver function normalised without sequelae; the adverse event of LFT increased was resolved on 17 Apr 2017 (Study Day 28). He was subsequently discharged home from hospital. Elevation in ALT is often seen in young infants, possibly due to rapid bone turnover and is rarely of clinical significance. This case was not considered as a Hy's Law case since the patient had risk factors such as underlying congenital heart disease, concurrent abdominal pathology, long-term TPN use and in addition several concomitant medications such as piperacillin/tazobactam, oxycodone, propranolol, vancomycin that could explain the transient abnormal liver test results.

Vital signs

Mean changes from baseline to end of study, or from baseline to interim timepoints, were not considered to be clinically relevant for any of the measured vital signs parameters.

Audiology

Due to the age and underlying illness of participants in the study population, audiology testing was difficult to perform and interpret in the cohorts that were studied. To evaluate the audiology investigations such as response to noise, acoustic reflex and investigation of the auditory brainstem response. Furthermore, the ear canal was thoroughly investigated. At day 28, none of the eight paediatric subjects was reported with signs of ototoxicity due to dalbavancin.

2.3.3. Discussion on clinical aspects

The MAH has submitted the final report for PIP study 6 (DAL-PK-02) and this AR includes results obtained in the study. It is noted that the study was terminated and that this has been agreed with the PDCO. No dose proposal is included since the MAH will use PK data from both study 6 and 7 (ongoing) and thereafter propose a dose for this paediatric age group. It is noted that a type II variation including this data is planned to be submitted by December 2022.

The included number of subjects included in this study is limited, mainly due to recruitment issues. The MAH has argued that the variability of PK of dalbavancin is low and that the ongoing PIP Study 7 is expected to provide additional PK data from up to 10 subjects below 3 months of age.

Overall, the implemented study design in terms of PK as well as the obtained PK results appear adequate. A total of 8 participants received dalbavancin 22.5 mg/kg (single IV infusion over 30 minutes) in the present study. It has been noted that the average CL of dalbavancin in Cohort 1 (participants aged > 28 days to < 3 months) appeared to be greater than the typical value of CL in adult patients, while $AUC_{0\text{-}120}$ was lower in all studied cohorts than in adults receiving 1500 mg. The obtained PK data from this study are intended to be combined with additional data from clinical studies of dalbavancin in paediatric patients (Studies A8841004, DUR001-106, DUR001-306) in a population PK analysis (to be reported separately by the MAH). The updated population PK model is then intended to be used to conduct PK/PD target attainment simulations to support dosing of dalbavancin in paediatric patients from birth to less than 18 years.

One subject experienced an event of increased ALT and bilirubin which was considered related to study drug but was not classified as a Hy's law case because there were other possible explanations to the LFT than liver injury. The subject did not present with clinical signs related to the increased liver transaminases, which went back to normal during the study period. However, increased liver transaminases are a known adverse event that may occur in adults treated with dalbavancin and it cannot be excluded that this event was to some extent related to dalbavancin.

Even though there are challenges to evaluating audiology in infants and babies, none of the performed investigations suggested that the treatment with dalbavancin would have had impact on the audiology in those infants. It should, however, be kept in mind that the included number of paediatric subjects in this study are limited and at this stage no firm conclusion regarding safety in paediatric subjects can therefore be drawn based on this study only.

3. CHMP overall conclusion and recommendation

This report reviews data obtained from the PIP Study 6 (DAL-PK-02) including 8 paediatric subjects below 3 months of age with known or suspected bacterial infection that has been treated with a single intravenous infusion of dalbavancin at the dose of 22.5 mg/kg body weight. The main purpose was to evaluate the PK profile, with plasma concentration as primary endpoint. As secondary endpoint the safety and tolerability were evaluated.

The safety signals observed in this study do not suggest that any further actions regarding PIP Study 7 are required at this stage.

According to the PIP EMEA-000016-PIP01-07-M07, dose selection in paediatric subjects below 3 months of age will be based on PK-results from both PIP Study 6 and PIP Study 7. Since PIP study 7 is still ongoing, no dose proposal has been included within this application.

☒ Fulfilled:

No regulatory action required.

Annex 1 - Line listing of all the studies included in the development program, listed by chronological date of completion:

Non-clinical studies

Product Name: Xydalba

Active substance: dalbavancin

Study title	Study number	Date of completion	Date of submission of final study report
Dose range finding study with dalbavancin in neonatal rat	2	Oct 2007	Completed study at the time of the PDCO review
Definitive juvenile rat toxicology study of dalbavancin	3	May 2008	Completed study at the time of the PDCO review

Clinical studies

Product Name: Xydalba

Active substance: dalbavancin

Study title	Study number	Date of completion	Date of submission of final study report
Paediatric pharmacokinetic study for the determination of pharmacokinetics of dalbavancin in paediatric patients aged 12 to less than 18 years for selection of dosing for a Phase 3 study for children with acute bacterial skin and skin structure infections.	4 (A8841004)	Sept 2009	Dec 2009
Paediatric pharmacokinetic study for the determination of pharmacokinetics of dalbavancin in paediatric patients aged 3 months to less than 12 years for selection of dosing for a Phase 3 study in children with acute bacterial skin and skin structure infections	5 [A8841013 (dur001-106)]	April 2015	Nov 2015
Paediatric pharmacokinetic study for the determination of pharmacokinetics of dalbavancin in paediatric patients aged less than 3 months with suspected or confirmed bacterial infections for selection of dosing	6 [A8841014 (DUR001-107)]	Oct 2019	April 2020 (Current submission)