29 January 2026
EMADOC-1700519818-2531410
Human Medicines Division

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

Vaborem

meropenem / vaborbactam

Procedure no: EMEA/H/C/004669/II/0020

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	1 December 2025	1 December 2025
☐	CHMP Rapporteur AR	5 January 2026	7 January 2026
☐	CHMP comments	19 January 2026	N/A
☐	Updated CHMP Rapporteur AR	22 January 2026	N/A
☒	CHMP outcome	29 January 2026	29 January 2026

Table of contents

1. Introduction

On 14 October 2025, the MAH submitted a completed paediatric study for Vaborem, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s) agreed upon in the EU Paediatric Investigation Plan (PIP) (P/0530/2023) and modified in EMA/PE/0000231022

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that REMPEX-507, An Open-label, Dose-finding, Pharmacokinetics, Safety, and Tolerability Study of a Single-dose Infusion of Meropenem-vaborbactam in Paediatric Subjects from Birth to Less than 18 Years of Age with Serious Bacterial Infections, is part of a clinical development program. The variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted after completion of studies 7 and 8 of the program. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Meropenem-vaborbactam was initially provided as separate vials of meropenem and vaborbactam. From August 2017, meropenem-vaborbactam was provided as a single-vial product, which consisted of a sterile powder blend of crystalline meropenem trihydrate, crystalline vaborbactam, plus lyophilised sodium carbonate. It was supplied in single-use vials containing 1174 mg of meropenem trihydrate plus 1030 mg of vaborbactam. When reconstituted as instructed, each vial delivered 1000 mg meropenem and 1000 mg of vaborbactam.

The Sponsor (or designee) packaged, labelled, and supplied meropenem-vaborbactam according to applicable regulatory requirements.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- REMPEX-507, An Open-label, Dose-finding, Pharmacokinetics, Safety, and Tolerability Study of a Single-dose Infusion of Meropenem-vaborbactam in Paediatric Subjects from Birth to Less than 18 Years of Age with Serious Bacterial Infections

2.3.2. Clinical study

REMPEX-507, An Open-label, Dose-finding, Pharmacokinetics, Safety, and Tolerability Study of a Single-dose Infusion of Meropenem-vaborbactam in Paediatric Subjects from Birth to Less than 18 Years of Age with Serious Bacterial Infections

Description

The study was a Phase 1 study to evaluate the PK, safety, and tolerability of meropenem-vaborbactam in paediatric participants with suspected or confirmed bacterial infection receiving antibiotic therapy or receiving perioperative prophylactic use of antibiotics. The goal of this study was to determine the safety and dose of meropenem-vaborbactam that achieves comparable exposure to standard dosing for treatment of UTIs in adults.

The report (data cut-off, 26 June 2025) includes data from Cohorts 1, 2a, 2b, 3, and 6, plus data for 4 participants in Cohort 4.

Methods

Study participants

The original study protocol (29 February 2016) was designed to enrol up to 56 participants in 5 age-based cohorts, to be sequentially enrolled after evaluation by a Data Safety Monitoring Board (DSMB) and following their recommendation to proceed. Participants were male or female from birth to <18 years of age, hospitalised, in stable condition, and receiving systemic antibiotics for a known or suspected bacterial infection; or receiving perioperative prophylactic antibiotics. Participants with signs of sepsis or other conditions likely to interfere with the study or be put at risk were excluded.

Participants were to receive a weight-based dose of 40 mg/kg of meropenem and 40 mg/kg of vaborbactam. At a body weight of 50 kg and above, participants were to receive 2 g of meropenem and 2 g of vaborbactam.

Background

The goal of the study in paediatric participants (Study 4 - REMPEX-507) was to determine the dose of Vaborem that achieves the comparable exposure, namely area under the curve of the plasma concentration (AUC) of meropenem and vaborbactam that have been proven in adults to be safe and efficacious for treatment of UTIs.

Under the assumptions that adults and children have (i) a similar disease and disease progression, (ii) a similar response to treatment, and (iii) a similar PK-PD relationship, children are expected to respond similarly to adults provided that the same exposure levels to meropenem and vaborbactam are achieved.

The selection of dose for the lowest age from birth to < 3 months (not treated in the Study 4), meropenem data available from the literature have been also used in the analysis to cover the entire age range of the paediatric population.

Treatments

The investigational study drug, meropenem-vaborbactam, was administered to all participants as a single-dose IV infusion, diluted in normal saline and infused over 3 hours. A pharmacist was responsible for providing study drug to the study personnel for administration. The study drug was provided ready for IV infusion. Each participant received an infusion by programmable infusion pump while seated or semi-recumbent in bed. The times at which the infusion was started and stopped were recorded. Instances where a dose was interrupted by more than 10 minutes were noted in the source documents, including the reason for interruption. Dosing time was relative to the start of the infusion.

Objectives

The primary objectives of the study were the following:

- To evaluate the PK of meropenem and vaborbactam following a single IV dose of meropenem-vaborbactam in paediatric participants from birth to <18 years for the purposes of dose-finding.

- To evaluate the safety and tolerability of a single IV dose of meropenem-vaborbactam in paediatric participants from birth to <18 years for the purposes of dose-finding.

Outcomes/endpoints

The primary endpoints were the following:

- PK parameters (AUC, maximum observed plasma concentration [C_{max}], time to reach maximum observed plasma concentration [Tmax], clearance [CL], half-life [$t_{1/2}$], minimum observed plasma concentration [C_{min}], and volume of distribution at steady state [Vss]) of meropenem-vaborbactam after a single IV dose in paediatric participants.

- Safety and tolerability of a single IV dose of meropenem-vaborbactam in paediatric participants, as assessed by AEs, changes in clinical laboratory parameters, vital signs, and electrocardiograms (ECGs).

Sample size

The original study protocol (29 February 2016) was designed to enrol up to 56 participants in 5 age-based cohorts, to be sequentially enrolled after evaluation by an external independent Data Safety Monitoring Board (DSMB) and following their recommendation to proceed. Participants were to receive a weight-based dose of 40 mg/kg of meropenem and 40 mg/kg of vaborbactam. At a body weight of 50 kg and above, participants were to receive 2 g of meropenem and 2 g of vaborbactam.

During DSMB and Sponsor review of the safety and PK data from Cohort 2, it was observed that clearance increased and exposure decreased relative to adults with higher body weights when moving from Cohort 1 (12 to <18) to Cohort 2 (6 to <12). Based on the reduced exposure of both meropenem and vaborbactam observed in Cohort 2, the dose was increased from 40 mg/kg to 60 mg/kg (up to a maximum of 2 g each of meropenem and vaborbactam) in 4 additional participants in Cohort 2 (referred to as Cohort 2b) and in Cohort 3. Exposures for the additional 4 participants in Cohort 2b continued to trend lower, while exposures in Cohort 3 remained on target. Therefore, the DSMB recommended enrolling Cohort 4 (3 months to <2 years) at the same dose of 60 mg/kg, and to evaluate a new cohort of participants (Cohort 6) aged 2 to <12 years and weighing ≤35 kg, dosed at 80 mg/kg (up to a maximum of 2 g each for meropenem and vaborbactam).

In the final protocol (Amendment 4, 20 September 2022), the plan was to enrol approximately 67 participants at 10 to 15 centres to receive a single-dose IV infusion of meropenem-vaborbactam. Age cohorts were enrolled sequentially, except for Cohort 6, which was planned to enrol simultaneously with Cohort 4.

Final cohorts to be studied were:

- Cohort 1 (target n=8): 12 to <18 years of age (complete/closed with 8 participants at
- 40 mg/kg)
- Cohort 2 (target n=12): 6 to <12 years of age (complete/closed with 8 participants at 40 mg/kg and 4 participants at 60 mg/kg)
- Cohort 3 (target n=8): 2 to <6 years of age (complete/closed with 8 participants at 60 mg/kg)
- Cohort 4 (target n=8): 3 months to <2 years of age (4 participants at 60 mg/kg)
- Cohort 5 (target n=24): birth to <3 months of age (no participants enrolled)
    - Group A (n=6): GA <32 weeks, PNA <2 weeks
    - Group B (n=6): GA <32 weeks, PNA >2 weeks
    - Group C (n=6): GA >32 weeks, PNA <2 weeks
    - Group D (n=6): GA >32 weeks, PNA >2 weeks
- Cohort 6 (target n=7): 2 to <12 years of age weighing ≤35 kg (complete/closed with 7 participants at 80 mg/kg)

Following early termination of the study, a total number of 45 participants were enrolled, and 39 participants were treated.

Randomisation and blinding (masking)

Not applicable as the study was single arm, open label.

Statistical Methods

The sample size was selected to ensure enough PK data were collected to provide adequate PK parameter estimates for each age cohort and group while minimising the number of paediatric participants exposed to meropenem-vaborbactam.

Analysis Populations

The Safety Population included all enrolled participants who received any study drug exposure. This was the primary population for safety analysis.

The PK Population included all participants in the Safety Population who preferably completed all PK blood draws, but at a minimum, completed at least 1 post-dose PK blood draw. This was the primary population for PK analysis.

Results

Participant flow

Recruitment

A total of 45 participants were screened for the study, and 6 participants (13.3%) failed screening. Reasons for screen failure included exclusion criteria met (3 participants [50.0%]), did not receive treatment (1 participant [16.7%]), and withdrew consent (1 participant [16.7%]). In addition, 1 participant was inadvertently enrolled into the study into a cohort that was not open and was, therefore, discontinued as a screen failure and could not be assigned to a cohort.

Table 1. Enrolment by Cohort

Cohort (Target Enrollment)	Age	Dose (Meropenem and Vaborbactam)[1]	Status (Actual Enrollment)
Cohort 1 (n=8)	12 to <18 years	40 mg/kg and 40 mg/kg	Completed (n=8)
Cohort 2 (n=12)	6 to <12 years	Cohort 2a: 40 mg/kg and 40 mg/kg Cohort 2b: 60 mg/kg and 60 mg/kg	Completed (n=12); Cohort 2a: n=8; Cohort 2b: n=4)
Cohort 3 (n=8)	2 to <6 years	60 mg/kg and 60 mg/kg	Completed (n=8)
Cohort 4 (n=8)	3 months to <2 years	60 mg/kg and 60 mg/kg	Completed (n=4)[2]
Cohort 5 (n=24)	Birth to <3 months[3]	To be determined	Completed (n=0)
Cohort 6 (n=8)	2 to <12 years and ≤35 kg	80 mg/kg and 80 mg/kg	Completed (n=7)

n = number of participants.
1 Up to a maximum dose of 2 g meropenem and 2 g vaborbactam.
2 Data for the 4 participants who completed Cohort 4 are included in this CSR.
3 Includes 0–28 day neonates.
Source: Table 1.2

Baseline data

Demographics and other baseline characteristics are summarised in the tables below.

Overall, the majority of participants were male and white, and just over half of participants were not Hispanic or Latino. Most participants weighed <50 kg. The mean BMI-for-age (Z-score) was 0.150 (range: −2.14 to 2.86).

Table 2. Participant Demographics (Safety Population)

Category	Cohort 1 (40 mg/kg) (N=8)	Cohort 2a (40 mg/kg) (N=8)	Cohort 2b (60 mg/kg) (N=4)	Cohort 3 (60 mg/kg) (N=8)	Cohort 4 (60 mg/kg) (N=4)	Cohort 6 (80 mg/kg) (N=7)	Total (N=39)
Age (years)							
Mean (SD)	15.19 (1.780)	8.95 (1.482)	8.59 (1.745)	4.38 (0.881)	1.17 (0.590)	6.08 (2.885)	7.94 (4.708)
Median	15.44	8.77	8.64	4.47	1.19	6.39	7.60
Q1, Q3	13.98, 16.35	8.37, 9.95	7.14, 10.05	3.71, 5.05	0.76, 1.58	2.53, 9.01	4.39, 10.81
Min, Max	12.2, 17.8	6.4, 11.0	6.7, 10.4	3.0, 5.6	0.4, 1.9	2.2, 9.6	0.4, 17.8
Gender, n (%)							
Male	5 (62.5)	2 (25.0)	2 (50.0)	3 (37.5)	4 (100)	7 (100)	23 (59.0)
Female	3 (37.5)	6 (75.0)	2 (50.0)	5 (62.5)	0	0	16 (41.0)
Race, n (%)							
White	6 (75.0)	7 (87.5)	2 (50.0)	5 (62.5)	2 (50.0)	3 (42.9)	25 (64.1)
Black or African American	0	0	0	0	1 (25.0)	1 (14.3)	2 (5.1)
Asian	0	0	0	1 (12.5)	0	0	1 (2.6)
American Indian or Alaska Native	2 (25.0)	1 (12.5)	2 (50.0)	2 (25.0)	0	2 (28.6)	9 (23.1)
Native Hawaiian or Other Pacific Islander	0	0	0	0	1 (25.0)	1 (14.3)	2 (5.1)
Ethnicity, n (%)							
Hispanic or Latino	1 (12.5)	4 (50.0)	4 (100)	3 (37.5)	1 (25.0)	5 (71.4)	18 (46.2)
Not Hispanic or Latino	7 (87.5)	4 (50.0)	0	5 (62.5)	3 (75.0)	2 (28.6)	21 (53.8)
Weight (kg)							
Mean (SD)	54.94 (9.717)	31.21 (11.601)	26.63 (7.319)	18.58 (3.306)	10.60 (2.028)	21.21 (7.159)	29.11 (16.425)
Median	53.70	27.90	25.30	18.50	11.0	20.80	24.20
Q1, Q3	48.65, 61.10	25.55, 32.85	20.75, 32.50	15.60, 20.70	9.25, 11.95	14.10, 26.50	18.50, 37.30
Min, Max	41.2, 71.4	19.8, 57.3	20.1, 35.8	14.8, 24.2	7.8, 12.6	12.7, 33.5	7.8, 71.4
Weight Group, n (%)							
<50 kg	3 (37.5)	7 (87.5)	4 (100)	8 (100)	4 (100)	7 (100)	33 (84.6)
≥50 kg	5 (62.5)	1 (12.5)	0	0	0	0	6 (15.4)

Category	Cohort 1 (40 mg/kg) (N=8)	Cohort 2a (40 mg/kg) (N=8)	Cohort 2b (60 mg/kg) (N=4)	Cohort 3 (60 mg/kg) (N=8)	Cohort 4 (60 mg/kg) (N=4)	Cohort 6 (80 mg/kg) (N=7)	Total (N=39)
Height (cm)							
Mean (SD)	166.94 (9.552)	130.50 (12.212)	126.93 (12.153)	108.1 (8.753)	77.88 (13.518)	112.64 (19.041)	124.41 (28.988)
Median	165.50	127.00	127.50	107.00	80.50	116.00	124.00
Q1, Q3	158.25, 174.50	124.00, 137.00	118.35, 135.50	100.75, 114.00	68.25, 87.50	92.00, 132.50	106.00, 141.00
Min, Max	157.0, 182.0	114.0, 154.0	111.7, 141.0	98.0, 123.4	59.5, 91.0	86.0, 137.0	59.5, 182.0
BMI (kg/m^2)							
Mean (SD)	19.82 (3.918)	17.78 (2.936)	16.27 (1.887)	15.80 (1.112)	17.87 (3.322)	16.40 (1.534)	17.40 (2.882)
Median	18.74	17.38	16.69	15.82	17.14	16.29	16.46
Q1, Q3	16.68, 22.49	15.53, 18.52	14.90, 17.64	15.19, 16.18	15.19, 20.55	15.46, 17.17	15.72, 18.02
Min, Max	16.3, 26.4	15.2, 24.2	13.7, 18.0	14.2, 17.9	15.2, 22.0	14.1, 19.1	13.7, 26.4
BMI-for-age (Z-score)							
Mean (SD)	−0.447 (1.3214)	0.452 (0.6642)	−0.059 (0.9240)	0.205 (0.8721)	0.748 (1.8097)	0.201 (0.8861)	0.150 (1.0633)
Median	−0.671	0.541	0.352	0.396	0.558	0.409	0.393
Q1, Q3	−1.370, 0.519	−0.092, 0.762	−0.587, 0.470	−0.443, 0.685	−0.747, 2.244	−0.015, 0.638	−0.508, 0.755
Min, Max	−2.14, 1.60	−0.45, 1.65	−1.44, 0.50	−1.19, 1.55	−0.99, 2.86	−1.63, 1.18	−2.14, 2.86

BMI = body mass index; CDC = Centers for Disease Control and Prevention; Max = maximum; Min = minimum; N = number of participants; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; WHO = World Health Organization.

Notes: BMI [kg/m^2] = weight [kg] / (height [m]**2). Z-scores are calculated as Z = [(BMI/M)**L) – 1] / (S*L) based on the LMS method and CDC/WHO growth charts.

Source: Table 2.1

Table 3. Baseline Infection (Safety Population)

Category	Cohort 1 (40 mg/kg) (N=8)	Cohort 2a (40 mg/kg) (N=8)	Cohort 2b (60 mg/kg) (N=4)	Cohort 3 (60 mg/kg) (N=8)	Cohort 4 (60 mg/kg) (N=4)	Cohort 6 (80 mg/kg) (N=7)	Total (N=39)
Participants with Number of Infections[1], n (%)							
1	6 (75.0)	5 (62.5)	2 (50.0)	5 (62.5)	2 (50.0)	6 (85.7)	26 (66.7)
2	1 (12.5)	1 (12.5)	2 (50.0)	0	2 (50.0)	0	6 (15.4)
≥3	1 (12.5)	2 (25.0)	0	2 (25.0)	0	0	5 (12.8)
Days from Last Infection Onset to Treatment Start[1]							
n	7	8	3	6	3	6	33
Mean (SD)	12.1 (7.65)	7.8 (3.69)	6.3 (3.51)	13.2 (7.17)	8.0 (3.61)	10.7 (6.02)	10.1 (5.92)
Median	8.0	8.0	6.0	11.0	7.0	12.5	9.0
Q1, Q3	7.0, 20.0	5.0, 10.5	3.0, 10.0	7.0, 18.0	5.0, 12.0	4.0, 15.0	7.0, 13.0
Min, Max	7, 26	2, 13	3, 10	7, 25	5, 12	3, 17	2, 26
Baseline Suspected Bacterial Infection(s)[2], n (%)							
Other	5 (62.5)	5 (62.5)	0	4 (50.0)	1 (25.0)	3 (42.9)	18 (46.2)
Staphylococcus aureus (gram +)	2 (25.0)	1 (12.5)	3 (75.0)	2 (25.0)	0	1 (14.3)	9 (23.1)
Missing	0	2 (25.0)	1 (25.0)	3 (37.5)	2 (50.0)	0	8 (20.5)
Pseudomonas aeruginosa (gram −)	1 (12.5)	0	1 (25.0)	1 (12.5)	1 (25.0)	1 (14.3)	5 (12.8)
Staphylococcus (Methicillin Susceptible) (gram +)	0	1 (12.5)	1 (25.0)	0	0	1 (14.3)	3 (7.7)
Streptococcus pyogenes (gram +)	0	1 (12.5)	0	1 (12.5)	1 (25.0)	1 (14.3)	4 (10.3)
Staphylococcus Coagulase Negative (Gram +)	2 (25.0)	0	0	0	0	0	2 (5.1)
Staphylococcus epidermidis (gram +)	1 (12.5)	0	0	1 (12.5)	0	0	2 (5.1)
Streptococcus Group A (gram +)	1 (12.5)	1 (12.5)	0	0	0	0	2 (5.1)
Bacteroides fragilis (gram −)	1 (12.5)	0	0	0	0	0	1 (2.6)
Escherichia coli (gram −)	1 (12.5)	0	0	0	1 (25.0)	0	2 (5.1)
Staphylococcus aureus (Methicillin Resistant) (gram +)	1 (12.5)	0	0	0	0	0	1 (2.6)

+ = positive; − = negative; Max = maximum; Min = minimum; N = number of participants; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
[1] Counted on a participant basis.
[2] A participant might have multiple infections. Multiple pathogens could be identified for each infection.
Source: Table 2.3.1

Number analysed

A total of 39 participants were enrolled into the study. All enrolled participants were included in the Safety Population and completed the study.

All treated participants had at least one plasma sample available for measurement of meropenem and vaborbactam concentrations and constitute the PK population.

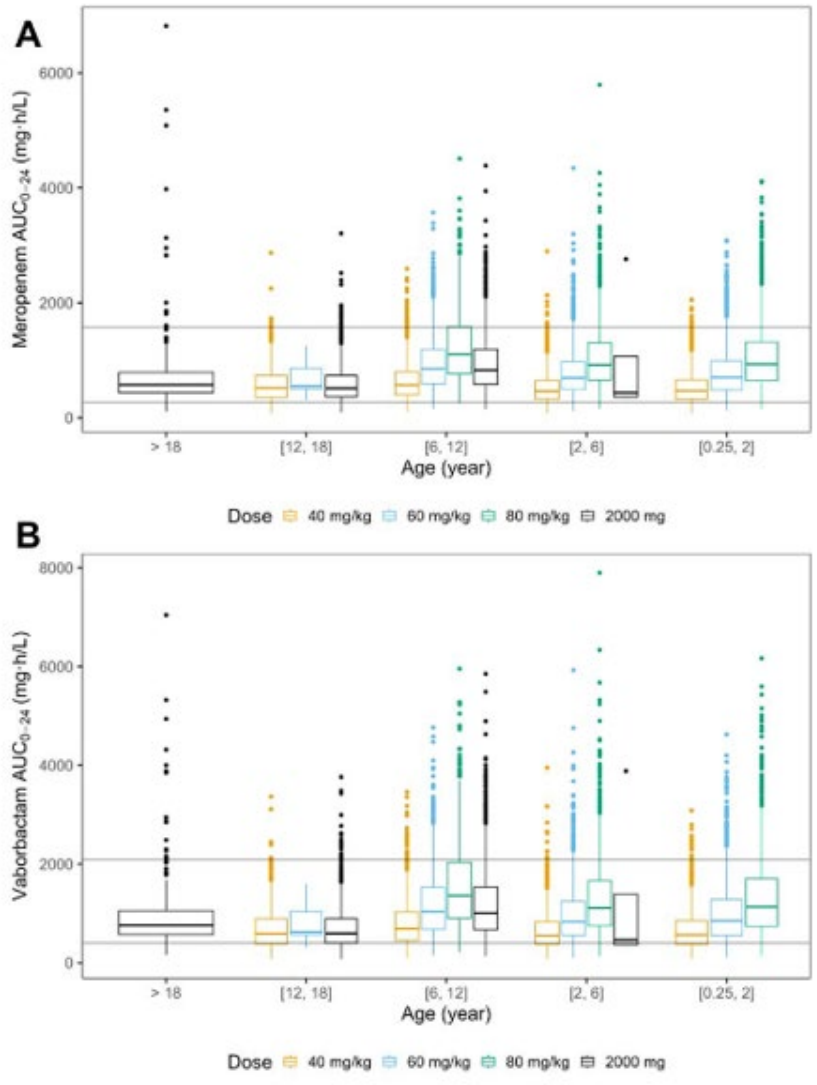
PK results

At the cut-off date of the report, plasma samples for concentration measurements of meropenem and vaborbactam were available from 38 out of the 39 treated participants of the study (Study 4 - REMPEX-507), leading to a total of 114 concentrations of both meropenem and vaborbactam. These data have been subject to popPK and target attainment analyses (VABO-PKPD-02) that support the selection of the paediatric doses of meropenem and vaborbactam comparable to the ones showing to be safe and efficacious in adults, in terms of both systemic exposure and probability of target attainment (PTA).

Simulations of meropenem and vaborbactam concentrations in the virtual population of children aged 3 months and older showed that for meropenem the target exposures (AUC_{0-24}) were reached after 3-h IV infusions of (i) 40, 60, and 80 mg/kg in children aged 3 months to <12 years, and (ii) 40 and 60 mg/kg in children aged 12 years to <18 years (Figure 1).

Probability of target attainment *(*PTA) analysis associated with %T>MIC ≥45% target at 8 mg/L MIC in the virtual paediatric population showed that 3.5-h IV infusion of 40 mg/kg of both meropenem and vaborbactam Q8h resulted in percent PTA ≥90% for children aged ≥3 months and with body weight < 50 kg (Table 4). With regard to neonates aged 3 months and younger, PTA analysis associated with %T>MIC ≥45% target at 8 mg/L MIC for this group showed that the following two doses resulted in percent PTA ≥90% for neonates from birth to <3 months: (i) 3.5-h IV infusion of 20 mg/kg of both meropenem and vaborbactam Q8h, and (ii) 3-h IV infusion of 30 mg/kg of both meropenem and vaborbactam Q8h (Table 5).

Figure 1. Boxplots of meropenem (**A**) and vaborbactam (**B**) $AUC_{0\text{-}24}$ for adult and paediatric patients older than 3 months. Exposures in adults were taken from simulations in the ICPD report **[4]**, whereas exposures in children were simulated using the updated paediatric popPK models (with a 3-hour IV infusion) and the virtual population of 8000 children (2000 for each age group). A maximum dose of 2000 mg of both meropenem and vaborbactam was given to subjects whose weight-based doses were above 2000 mg. Horizontal grey lines show the $AUC_{0\text{-}24}$ target ranges for the paediatric population, derived from Phase III clinical studies exposure data in adults (5^{th} - 95^{th} percentiles **[4]**). Target ranges are 270-1570 mg*h/L and 400-2090 mg*h/L for meropenem and vaborbactam, respectively.



$AUC_{0\text{-}24}$: area under the plasma concentration-time curve in the 0-24 hour period.

*Probability of target attainment (*PTA) analysis associated with %T>MIC ≥45% target at 8 mg/L MIC in the virtual paediatric population showed that 3.5-h IV infusion of 40 mg/kg of both meropenem and vaborbactam Q8h resulted in percent PTA ≥90% for children aged ≥3 months and with body weight < 50 kg (Table 4).

Table 4. Percent probabilities of PK-PD target attainment relative to the 8 mg/L meropenem-vaborbactam MIC, associated with the %T>MIC> 45% target, for children aged 3 months and older. The maximum dose of both meropenem and vaborbactam is capped to 2000 mg. Children whose weight-based doses are calculated to be higher than 2000 mg receive only 2000 mg of each moiety.

Age and weight group	N	40 mg/kg of both meropenem and vaborbactam, q8h, 3 h IV infusion			60 mg/kg of both meropenem and vaborbactam, q8h, 3 h IV infusion			40 mg/kg of both meropenem and vaborbactam, q8h, 3.5 h IV infusion		
		Ent	KPC	PSA	Ent	KPC	PSA	Ent	KPC	PSA
[0.25 y – 2 y]	2000	80%	80%	79%	87%	87%	86%	94%	95%	94%
[2 y– 6 y]	2000; 1996<25kg	80%	79%	78%	87%	87%	86%	95%	95%	95%
[6 y– 12 y] (a)	1980<50kg; 1390<33.3kg; 582<25kg	87%	87%	87%	93%	93%	93%	98%	98%	98%
[12 y– 18 y] (a)	714<50kg; 10<33.3kg, 0<25kg	83%	83%	82%	90%	90%	90%	96%	96%	96%
[6 y– 18 y] (b)	1306≥50kg; 2600≥33.3k	86%	86%	85%	87%	87%	86%	96%	96%	96%

With regard to neonates aged 3 months and younger, PTA analysis associated with %T>MIC ≥45% target at 8 mg/L MIC for this group showed that the following two doses resulted in percent PTA ≥90% for neonates from birth to <3 months: (i) 3.5-h IV infusion of 20 mg/kg of both meropenem and vaborbactam Q8h, and (ii) 3-h IV infusion of 30 mg/kg of both meropenem and vaborbactam Q8h (Table 5).

Table 5. Percent probabilities of PK-PD target attainment relative to the 8 mg/L meropenem-vaborbactam MIC, associated with the %T>MIC> 45% target, for children aged 3 months and younger.

Age group (years)	N	20 mg/kg of both meropenem and vaborbactam, 3-h IV infusion, every 8h			30 mg/kg of both meropenem and vaborbactam, q8h, 3 h IV infusion			20 mg/kg of both meropenem and vaborbactam, q8h, 3.5 h IV infusion			30 mg/kg of both meropenem and vaborbactam, q8h, 3.5 h IV infusion		
		Ent	KPC	PSA	Ent	KPC	PSA	Ent	KPC	PSA	Ent	KPC	PSA
preterm PNA < 14d	1020	99%	99%	99%	100%	100%	100%	100%	99%	99%	100%	100%	100%
preterm PNA ≥ 14d	2730	94%	94%	94%	97%	97%	97%	97%	97%	97%	99%	99%	99%
full term PNA < 14d	2000	99%	99%	99%	100%	100%	100%	100%	100%	100%	100%	100%	100%
full term PNA ≥ 14d	2000	85%	85%	83%	93%	93%	93%	92%	92%	91%	98%	98%	98%

Ent: Enterobacterales, KPC: *Klebsiella Pneumonia Carbapenemases-producing Enterobacterales* PSA: *Pseudomonas aeruginosa*, GA: gestational age, PNA: post-natal age, q8h: every 8 hours

The selected three doses to be tested in the subsequent PK multiple dose study (PIP Study 8), currently ongoing, are: (i) 2 / 2g q8h over 3 hours IV infusion for children aged 3 months and older weighing more than 50 kg; (ii) 40 / 40 mg/kg, q8h over 3.5 hours IV infusion for children aged 3 months and older, weighing less than 50 kg, and (iii) 20 / 20 mg / kg q8h over 3.5 hours IV infusion, for neonates and infants aged less than 3 months.

Efficacy results

Not applicable, safety and pharmacokinetics only study.

Safety results

Extent of Exposure

All 39 participants (100%) received the full dose of meropenem-vaborbactam. The overall mean (SD) duration of study drug infusion was 3.09 (0.149) hours (range: 2.9 to 3.6 hours). The mean (SD) doses per cohort were as follows:

- Cohort 1 (40 mg/kg): 1940.0 (124.67) mg (range: 1640 to 2000 mg)

- Cohort 2a (40 mg/kg): 1218.5 (369.21) mg (range: 800 to 2000 mg)
- Cohort 2b (60 mg/kg): 1550.0 (385.23) mg (range: 1200 to 2000 mg)
- Cohort 3 (60 mg/kg): 1117.5 (194.92) mg (range: 900 to 1440 mg)
- Cohort 4 (60 mg/kg): 630.0 (114.89) mg (range: 480 to 720 mg)
- Cohort 6 (80 mg/kg): 1588.6 (387.62) mg (range: 1040 to 2000 mg)

Adverse Events

Of the 39 participants in the Safety Population, 10 (25.6%) experienced any TEAE. Three participants (7.7%) experienced any study drug-related TEAE. Of the 39 participants, 1 (2.6%) in Cohort 6 experienced a treatment-emergent SAE that was not considered by the Investigator to be related to treatment. No participants experienced any TEAE that led to study drug discontinuation, a fatal outcome, or was considered a treatment-emergent AESI.

Table 6. Overall Summary of Adverse Events (Safety Population)

Category	Cohort 1 (40 mg/kg) (N=8) n (%)	Cohort 2a (40 mg/kg) (N=8) n (%)	Cohort 2b (60 mg/kg) (N=4) n (%)	Cohort 3 (60 mg/kg) (N=8) n (%)	Cohort 4 (60 mg/kg) (N=4) n (%)	Cohort 6 (80 mg/kg) (N=7) n (%)	Total (N=39) n (%)
No. of Participants with Any AE	3 (37.5)	3 (37.5)	2 (50.0)	0	1 (25.0)	3 (42.9)	12 (30.8)
No. of Participants with Any TEAE	2 (25.0)	3 (37.5)	2 (50.0)	0	1 (25.0)	2 (28.6)	10 (25.6)
No. of Participants with Any Study Drug-Related[1] TEAE	1 (12.5)	1 (12.5)	1 (25.0)	0	0	0	3 (7.7)
No. of Participants with Any TEAE Leading to Study Drug Discontinuation	0	0	0	0	0	0	0
No. of Participants with Any Treatment-Emergent SAE	0	0	0	0	0	1 (14.3)	1 (2.6)
No. of Participants with Any AE Leading to Fatal Outcome	0	0	0	0	0	0	0
No. of Participants with Any Treatment-Emergent AESI	0	0	0	0	0	0	0

AE = adverse event; AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; N/n = number of participants; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Notes: MedDRA Version 19.0. TEAEs are AEs which occurred or whose severities worsened on or after the initiation of study drug.

[1] Includes AEs considered by the Investigator as definitely related or possibly related to the study drug.
Source: Table 4.1; Listing 4.1

TEAEs are summarised in Table 7 below. Of the 39 participants in the Safety Population, 10 participants (25.6%) experienced any TEAE; Cohort 1, n=2 (25.0%), Cohort 2a, n=3 (37.5%), Cohort 2b, n=2 (50.0%), Cohort 4, n=1 (25.0%), and in Cohort 6, n=2 (28.6%). Diarrhoea, nausea, transaminases increased, and vomiting (2 participants [5.1%] each) were the only TEAEs reported in >1 participant.

Table 7. Summary of TEAEs by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Cohort 1 (40 mg/kg) (N=8) n (%)	Cohort 2a (40 mg/kg) (N=8) n (%)	Cohort 2b (60 mg/kg) (N=4) n (%)	Cohort 3 (60 mg/kg) (N=8) n (%)	Cohort 4 (60 mg/kg) (N=4) n (%)	Cohort 6 (80 mg/kg) (N=7) n (%)	Total (N=39) n (%)
No. of Participants with Any TEAE	2 (25.0)	3 (37.5)	2 (50.0)	0	1 (25.0)	2 (28.6)	10 (25.6)
Gastrointestinal Disorders	0	2 (2.5)	0	0	0	1 (14.3)	3 (7.7)
Diarrhoea	0	2 (25.0)	0	0	0	0	2 (5.1)
Nausea	0	1 (12.5)	0	0	0	1 (14.3)	2 (5.1)
Vomiting	0	1 (12.5)	0	0	0	1 (14.3)	2 (5.1)
Abdominal Pain	0	1 (12.5)	0	0	0	0	1 (2.6)
Investigations	1 (12.5)	0	1 (25.0)	0	0	1 (14.3)	3 (7.7)
Transaminases Increased	0	0	1 (25.0)	0	0	1 (14.3)	2 (5.1)
Blood Pressure Diastolic Decreased	1 (12.5)	0	0	0	0	0	1 (2.6)
Blood and Lymphatic System Disorders	0	1 (12.5)	0	0	0	1 (14.3)	2 (5.1)
Eosinophilia	0	1 (12.5)	0	0	0	0	1 (2.6)
Leukocytosis	0	0	0	0	0	1 (14.3)	1 (2.6)
General Disorders and Administration Site Conditions	0	1 (12.5)	1 (25.0)	0	0	0	2 (5.1)
Chills	0	0	1 (25.0)	0	0	0	1 (2.6)
Pyrexia	0	1 (12.5)	0	0	0	0	1 (2.6)
Cardiac Disorders	0	0	0	0	0	1 (14.3)	1 (2.6)
Tachycardia	0	0	0	0	0	1 (14.3)	1 (2.6)
Infections and Infestations	0	0	0	0	0	1 (14.3)	1 (2.6)
Influenza	0	0	0	0	0	1 (14.3)	1 (2.6)
Musculoskeletal and Connective Tissue Disorders	1 (12.5)	0	0	0	0	0	1 (2.6)
Musculoskeletal Chest Pain	1 (12.5)	0	0	0	0	0	1 (2.6)
Musculoskeletal Pain	1 (12.5)	0	0	0	0	0	1 (2.6)
Neck Pain	1 (12.5)	0	0	0	0	0	1 (2.6)
Nervous System Disorders	0	0	0	0	0	1 (14.3)	1 (2.6)
Headache	0	0	0	0	0	1 (14.3)	1 (2.6)
Respiratory, Thoracic and Mediastinal Disorders	0	0	0	0	1 (25.0)	1 (14.3)	2 (5.1)
Epistaxis	0	0	0	0	0	1 (14.3)	1 (2.6)
Grunting	0	0	0	0	1 (25.0)	0	1 (2.6)

MedDRA = Medical Dictionary for Regulatory Activities; N/n = number of participants; TEAE = treatment-emergent adverse event.
Notes: MedDRA Version 19.0. Participants with multiple TEAEs are only counted once within each MedDRA level.
Source: Table 4.2

Eight participants (20.5%) experienced TEAEs that were mild in severity (Cohort 1, n=2 [25.0%], Cohort 2a, n=3 [37.5%], Cohort 2b, n=2 [50.0%], and Cohort 6, n=1 [14.3%]). One participant in Cohort 6 experienced a moderate TEAE (PT epistaxis), and 1 participant in Cohort 4 experienced a severe TEAE (PT grunting). The moderate unrelated TEAE of epistaxis was reported as an SAE:

- Participant between 2 to <12 years, weight range 12-34 kg (Cohort 6 [80 mg/kg]). On Day 8, the participant experienced a moderate SAE (prolonged hospitalisation) of epistaxis that had no reasonable possibility of being related to study drug (as assessed by the Investigator). The event resolved 5 days after onset with medical treatment including Factor VII and transfusions.

Three participants (7.7%) experienced a *study drug-related* TEAE (PTs blood pressure diastolic decreased, eosinophilia, and transaminases increased). One participant was in Cohort 1, 1 participant in Cohort 2a, and 1 participant in Cohort 2b. No study drug-related TEAE was reported in >1 participant. All 3 drug-related TEAEs were considered mild in intensity.

- Participant between 12 to <18 years, weight range 40 – 72 kg (Cohort 1 [40 mg/kg]). His blood pressure at baseline was 103/68 mmHg and decreased to 97/57 mmHg on Day 1 post-dose (Listing 5.1). On Day 3, his blood pressure was 91/54 mmHg.
- Participant between 6 to <12 years, weight range 19 - 58 kg (Cohort 2a [40 mg/kg]) with a mild, possibly related TEAE for eosinophilia. Participant between 6 to <12 years, weight range 20-36 kg (Cohort 2b [60 mg/kg]), with a mild, possibly related TEAE for increased transaminases.

Table 8. Summary of TEAEs Related to Study Drug by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Cohort 1 (40 mg/kg) (N=8) n (%)	Cohort 2a (40 mg/kg) (N=8) n (%)	Cohort 2b (60 mg/kg) (N=4) n (%)	Cohort 3 (60 mg/kg) (N=8) n (%)	Cohort 4 (60 mg/kg) (N=4) n (%)	Cohort 6 (80 mg/kg) (N=7) n (%)	Total (N=39) n (%)
No. of Participants with Any Study Drug-related[1] TEAE	1 (12.5)	1 (12.5)	1 (25.0)	0	0	0	3 (7.7)
Investigations	1 (12.5)	0	1 (25.0)	0	0	0	2 (5.1)
Blood Pressure Diastolic Decreased	1 (12.5)	0	0	0	0	0	1 (2.6)
Transaminases Increased	0	0	1 (25.0)	0	0	0	1 (2.6)
Blood and Lymphatic System Disorders	0	1 (12.5)	0	0	0	0	1 (2.6)
Eosinophilia	0	1 (12.5)	0	0	0	0	1 (2.6)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; TEAE = treatment-emergent adverse event.
Notes: MedDRA Version 19.0. Participants with multiple TEAEs are only counted once within each MedDRA level.
[1] Includes AEs considered by the investigators as possibly related to the study drug.
Source: Table 4.3

One participant in Cohort 4 experienced a severe TEAE (PT grunting) but this was not regarded as a serious AE. The event resolved on the date of occurrence and was assessed by the Investigator as not related to the study medication.

No treatment-emergent AESIs were reported. No TEAEs leading to study drug discontinuation were reported. No treatment-emergent AESIs were reported. No AEs leading to a fatal outcome were reported.

Clinical Laboratory Evaluation

Clinical laboratory testing was decentralised. All analyses were performed locally. Laboratory values assessed by the investigator as clinically relevant were required to be considered as an AE and reported. Detailed review of all continuous laboratory variables found no clinically significant treatment-related effects.

Vital Signs, Physical Findings, and Other Observations Related to Safety

No overall trends in mean vital sign parameters were observed. Vital signs for most individual participants did not shift significantly from baseline to Day 1 (post-dose) or Day 3. A shift from the normal range at baseline to PCS high or PCS low results on Day 1 post-dose or Day 3 was observed for some individual participants across all cohorts. None of these changes were reported as a SAE. One shift in vital signs was reported as a study drug-related TEAE: a participant in Cohort 1 experienced decreased diastolic blood pressure (from normal at baseline to PCS low at Day 1 and Day 3) of mild severity.

12-Lead Electrocardiograms

Two participants showed changes in ECG findings at Day 1 post-baseline as follows:

- Participant between 12 to <18 years, weight range 40-72kg (Cohort 1 [40 mg/kg]). At Day 1 post-dose, the participant had increased heart rate (103 bpm) from baseline (78 bpm) and ECG reported possible left atrial enlargement and sinus tachycardia. No TEAEs were reported. The participant completed the study.

- Participant between 6 to <12 years, weight range 19-58 kg (Cohort 2a [40 mg/kg]). At Day 1 post-dose, this participant had sinus bradycardia (66 bpm at baseline decreased to 59 bpm) and supraventricular extrasystoles. No TEAEs were reported. The participant completed the study.

Two participants had abnormal ECG findings at baseline that did not change on Day 1 post-baseline as follows:

- Participant between 2 to <6 years, weight range 14-25 kg (Cohort 3 [60 mg/kg]). At Day 1 post-dose of meropenem-vaborbactam, the ECG was unchanged with abnormal borderline prolonged QT, abnormal right QRS, right axis deviation, and right ventricular hypertrophy. The ECG findings were consistent with hypoplastic left heart syndrome. No TEAEs were reported. The participant completed the study.
- Participant between 3 months to <2 years, weight range 7-13 kg (Cohort 4 [60 mg/kg]). At Day 1 post-dose, this participant had deep Q wave in lead 6, possible left ventricular hypertrophy, prolonged QT (324 msec), and sinus tachycardia (154 bpm) (Listing 7.1). No TEAEs were reported. The participant completed the study.

2.3.3. Discussion on clinical aspects

This study is a Phase 1, open-label, dose-finding, PK, safety, and tolerability study in paediatric participants aged birth to <18 years with suspected or confirmed bacterial infection receiving antibiotic therapy or receiving perioperative prophylactic use of antibiotics. The study enrolled 39 participants aged 3 months to 18 years divided in 5 cohorts. Participants received a single dose of meropenem-vaborbactam and were evaluated for pharmacokinetics and safety. As the study was phase 1, no efficacy data were collected. No new safety concerns were identified.

The safety and pharmacokinetic data collected in the first clinical study included in the PIP (Study 4 – REMPEX-507) supports continuing the paediatric development by opening the PK and safety multiple dose study in children from birth to < 18 years of age (PIP Study 8) aiming to confirm the preliminary data collected in the single dose Study 4.

A future paediatric indication application is expected when data from PIP study 8 are available.

3. CHMP overall conclusion and recommendation

The completed study (Study 4 – REMPEX-507) submitted and assessed in this procedure forms part of a paediatric clinical development plan agreed with regulatory authorities and documented in in the product's EU PIP (EMA/PE/0000231022). Additional data from other ongoing and planned paediatric clinical studies, and modelling and simulation measures, are anticipated in due course.

From the submitted data, no need for regulatory action has been identified at this time.

☒ **Fulfilled:**

No regulatory action required.