22 April 2021
EMA/265651/2021
Human Medicines Division

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

Recarbrio

imipenem / cilastatin / relebactam

Procedure no: EMEA/H/C/004808/P46/003

Note

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

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1. Introduction

On 4th February 2021, the MAH submitted a completed paediatric study for Imipenem/Cilastatin/Relebactam (Recarbrio®), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This is a stand-alone Article 46 submission. A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that

Study P020MK7655A: Phase 1b, noncomparative, open-label, single IV dose study to evaluate the PK, safety, and tolerability of imipenem/cilastatin/relebactam in paediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative infections

is part of a paediatric clinical development program and is part of the PIP approved by the EMA (PIP EMEA-001809-PIP01-15-M02). The variation application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by the end of 2023. A line listing of all the concerned studies is annexed.

IMI/REL was initially approved in the EU in February 2020 for the treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options. Subsequently, in November 2020, IMI/REL was approved by the European Commission for the additional indication for treatment of HAP, including VAP, in adults and bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP, in adults.

2.2. Information on the pharmaceutical formulation used in the study

The formulation used in the submitted, completed study is the same single vial IMI/REL fixed-dose combination as was authorised in the EU for use in adults as of February 2020.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- *Study P020MK7655A: Phase 1b, noncomparative, open-label, single IV dose study to evaluate the PK, safety, and tolerability of imipenem/cilastatin/relebactam in paediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative infections.*

2.3.2. Clinical study

***Study P020MK7655A:* Phase 1b, noncomparative, open-label, single IV dose study to evaluate the PK, safety, and tolerability of imipenem/cilastatin/relebactam in paediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative infections.**

Description

Methods

Objective(s)

Primary objective: To obtain plasma PK data and characterize the PK profile of imipenem, cilastatin, and relebactam (REL) following administration of a single intravenous (IV) dose of IMI/REL in paediatric participants from birth to less than 18 years of age receiving standard-of-care antibacterial therapy for a confirmed or suspected gram-negative bacterial infection.

Secondary objective: To evaluate the safety and tolerability profile of a single IV dose of IMI/REL in paediatric participants from birth to less than 18 years of age receiving standard-of-care antibacterial therapy for a confirmed or suspected gram-negative bacterial infection.

Study design

This was an open-label, single-dose study to evaluate the pharmacokinetics (PK), safety, and tolerability of MK-7655A (IMI/REL) and to identify the appropriate dose in paediatric participants from birth to less than 18 years of age receiving standard-of-care antibacterial therapy for treatment of a confirmed or suspected gram-negative bacterial infection.

PK parameters were assessed for 6-12 hours following single IV dose and safety parameters were assessed for up to 24 hours, with a safety follow-up visit or telephone call at 14 ±2 days.

Once the first 3 PK evaluable participants were enrolled in each of Cohorts 1 through 3, enrolment in that cohort was paused and an interim PK and safety review was performed to decide on the dose for the remaining half of the cohorts. An aggregate PK and safety interim review was conducted when enrolment was completed in Cohorts 1 through 3 to determine the initial dose for Cohorts 4 and 5. Enrolment in Cohorts 4 and 5 was also done in parallel and similar interim reviews were subsequently conducted.

Study population /Sample size

Main Inclusion Criteria

1. Male or female from birth (at least 37 weeks postmenstrual age) to <18 years of age at screening.
2. Hospitalized and was currently receiving antibacterial treatment for confirmed or suspected gram-negative bacterial infection and expected to require hospitalization until at least 24 hours after completion of study drug administration. Participants who were not receiving antibacterial treatment for the qualifying infection at the time of screening were eligible for this study if either (1) they would be initiating antibacterial treatment for the qualifying infection prior to study drug administration, or (2) they had recently (within 48 hours prior to study drug administration) completed antibacterial treatment for the qualifying infection.
3. Clinically stable renal function at the time of screening that was judged to be within acceptable ranges for age, as measured by creatinine clearance and as defined in the study protocol
4. Sufficient intravascular access to receive study drug through an existing peripheral or central line.

Main Exclusion Criteria

1. Personal history of hypersensitivity to IMI or to any carbapenem, cephalosporin, penicillin, other β-lactam agent, or other BLIs.
2. Female, currently pregnant or breast feeding or had a positive serum β-hCG pregnancy test prior to administration of the study drug.
3. History of a seizure disorder (requiring ongoing treatment with anticonvulsive therapy or prior treatment with anticonvulsive therapy within the last 3 years).
4. Use or planned use of valproic acid or divalproex sodium within 2 weeks prior to screening or at any point between screening and 24 hours after the completion of study drug infusion.
5. Treatment or planned treatment with any carbapenem antibiotic within 48 hours prior to initiation of study drug infusion or at any point between administration of study drug and the last PK sample collection.
6. Use or planned use of any of the following medications, which are OAT1 or OAT3 inhibitors, within 1 week prior to screening or at any point between screening and the last PK sample collection: cimetidine, probenecid, indomethacin, mefenamic acid, furosemide or other loop diuretics (eg, bumetanide, torsemide, ethacrynic acid), angiotensin receptor blockers (eg, valsartan), and ketorolac.
7. Current diagnosis of cystic fibrosis, meningitis, or severe sepsis.
8. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might expose the participant to risk by participating in the study, confound the results of the study, or interfere with the participant's participation for the full duration of the study.
9. Expected to survive less than 72 hours after completion of study drug administration.
10. Any laboratory abnormality listed in the protocol at the time of screening (with the exception of values, as determined by the investigator, that would be part of normal physiologic process for a particular age group [eg, physiologic hyperbilirubinemia in a newborn]).
11. History of clinically significant renal, hepatic, or hemodynamic instability (defined as a requirement for pharmacological intervention to manage blood pressure in the 24 hour window prior to enrolment).
12. Planned use of cardiopulmonary bypass, extracorporeal membrane oxygenation, hemodialysis, or peritoneal dialysis during the study.
13. For Cohorts 1 through 3 only: Had weight outside of the 5^{th} to 95^{th} percentile based on age.
14. At the time of signing informed consent, a user of recreational or illicit drugs or had had a recent history (within the last year) of drug or alcohol abuse or dependence.
15. Planned blood transfusion within 24 hours of study treatment administration or expected before the end of the PK sampling.
16. Significant blood loss (≥5% of total blood volume) within 4 weeks before the screening visit. Total blood volume can be estimated as 80 mL/kg of body weight.

A total of at least 44 participants was planned to be enrolled in a staggered approach in the 5 Cohorts based on age:

- Cohort 1: Adolescents (age 12 to <18 years); at least 6 participants

- Cohort 2: Older children (6 to <12 years); at least 6 participants
- Cohort 3: Younger children (2 to <6 years); at least 6 participants
- Cohort 4: Infants and toddlers (3 months to <2 years); at least 8 participants, at least 4 of whom were <1 year of age
- Cohort 5: Neonates and young infants (birth to <3 months); at least 18 participants, who were further divided into the following age subcohorts:
    - 4 weeks to <3 months of age; at least 6 participants
    - 1 week to <4 weeks of age; at least 6 participants
    - <1 week of age; at least 6 participants.

Treatments

IMI/REL was administered as single IV infusion over 30 (±5) minutes (initial infusion duration for cohorts 1-3) or 60 (±5) minutes (initial infusion duration for cohorts 4-5). Dose varied based on age cohort and timing of enrolment (before/after interim reviews), with maximal dose not exceeding 500 mg IMI/ 250 mg REL:

Table 1. IMI/REL Initial doses by Age Cohort

Age Cohort	Age Range	IMI/REL Proposed Initial Dose[a]
1 (n=6)	12 to <18 years	15/7.5 mg/kg over 30 min
2 (n=6)	6 to <12 years	15/7.5 mg/kg over 30 min
3 (n=6)	2 to <6 years	15/7.5 mg/kg over 30 min
4 (n=8)	3 months to <2 years[b]	10/5 mg/kg over 60 min[c]
5 (n=18)	Birth to <3 months[d]	10/5 mg/kg over 60 min[c]

Abbreviations: IMI/REL: imipenem/cilastatin/relebactam

[a] The proposed initial doses were modified based on interim data as described in Section 5.2.1.2 of the study protocol [16.1.1]. The dose modifications for Cohorts 1 through 4 that occurred as a result of the first interim review in these cohorts are described in Section 5.2.1.2.1 of the study protocol [16.1.1]. Single IV doses for all cohorts will not exceed the adult maximum dose of 500 mg IMI and 250 mg REL.

[b] At least 4 participants in Cohort 4 will be <1 year of age.

[c] Initial doses of IMI/REL for participants in Cohorts 4 and 5 were selected based on PK modeling and simulation analyses, after incorporating observed PK data from Cohorts 1 through 3 (Section 5.2.1.2.1 of the study protocol [16.1.1]). Initial doses for Cohorts 4 and 5 were communicated to sites via a Protocol Clarification Letter.

[d] Cohort 5 will be further subdivided into the following 3 age subcohorts:

- 4 weeks to <3 months of age; at least 6 participants
- 1 week to <4 weeks of age; at least 6 participants
- <1 week of age; at least 6 participants

Source: CLINICAL STUDY REPORT P020MK7655A Table 9-1.

Study duration: 18 days from the signing of informed consent, including screening (up to 2 days) and follow-up (14 ±2 days).

Outcomes/endpoints

Primary endpoints:

- REL: plasma PK exposures such as area under the plasma concentration-time curve (AUC) and maximum concentration (C_{max}), PK parameters such as systemic clearance and central volume of distribution.
- Imipenem: %fT>MIC, plasma PK exposures such as AUC and C_{max}, PK parameters such as systemic clearance and central volume of distribution.
- Cilastatin: plasma PK exposures such as AUC and C_{max}.

Secondary endpoints:

Adverse events (AEs), clinical laboratory evaluations, Events of Clinical Interest (ECIs), vital sign measurements, and physical examinations.

Special attention was given to post-treatment visit (Visit 3) laboratory abnormalities, based on the toxicity grading, as described in the United States National Institutes of Health (US NIH) Division of Microbiology and Infectious Diseases (DMID) paediatric toxicity scale.

Statistical Methods

Collected PK samples were analysed using noncompartmental PK analysis (cilastatin) and population PK modelling (imipenem and REL). Actual times were used for the PK analyses. Summary PK parameters for all analytes were derived by Cohort levels, as allowed by the data.

Safety and tolerability were assessed by clinical review of all relevant parameters including incidence, severity, and type of AEs, changes in clinical laboratory tests, and changes from baseline in vital sign measurements at the interim reviews and the end of study. Descriptive and/or summary statistics were provided.

Results

Recruitment/ Number analysed

There were no major protocol amendments that are considered to affect the results of the study.

Study initiation date (first participant first visit): 06-Nov-2017

Study completion date (last participant last visit): 11-Aug-2020

Database lock date: 11-Sep-2020

Report date: 22-Jan-2021

As of the database lock date, 47 participants were allocated in the 5 Cohorts:

Table 2. Subject Disposition

	Cohort 1		Cohort 2		Cohort 3		Cohort 4 (1 to 2 years)		Cohort 4 (3 months to < 1 year)		Cohort 5 (4 weeks to < 3 months)		Cohort 5 (1 to < 4 weeks)		Cohort 5 (< 1 week)		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized																	4	
Participants in population	7		6		6		4		4		8		6		6		47	
Trial Disposition																		
Completed	7	(100.0)	6	(100.0)	6	(100.0)	4	(100.0)	4	(100.0)	7	(87.5)	6	(100.0)	6	(100.0)	46	(97.9)
Discontinued	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	1	(2.1)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	1	(2.1)
Subject Study Medication Disposition																		
Started	7		6		6		4		4		7		6		6		46	
Completed	7	(100.0)	6	(100.0)	6	(100.0)	4	(100.0)	4	(100.0)	7	(100.0)	6	(100.0)	6	(100.0)	46	(100.0)

Each subject is counted once for Trial Disposition, Subject Study Medication Disposition based on the latest corresponding disposition record.
Cohort 1=12 to <18 years
Cohort 2=6 to <12 years
Cohort 3=2 to <6 years
Cohort 4=3 months to <2 years
Cohort 5=birth to < 3 months

Source: CLINICAL STUDY REPORT P020MK7655A Table 10-1.

A total of 46 treated participants received a single dose infusion of IMI/REL.

Baseline data

The majority of participants were female (59.6%), white (78.7%), and of non-Hispanic or Latino ethnicity (83.0%). Low mean creatine clearance observed among participants in Cohort 5 (<3 months of age) was most likely the result of functional immaturity of the developing newborn kidneys.

The 4 most frequently reported medical history conditions in the safety population by PT included anaemia (19.6%), varicella infection (13.0%), respiratory failure (8.7%), and hypoxic-ischaemic encephalopathy (6.5%). The 4 most frequently reported prior medications in the safety population included acetaminophen (43.5%), ampicillin (23.9%), gentamicin (21.7%), and cefoperazone sodium (+) sulbactam sodium (21.7%). The 4 most frequently reported concomitant medications in the safety population included gentamicin (19.6%), acetaminophen (19.6%), dextrose (15.2%), and cholecalciferol (15.2%).

Pharmacokinetic results

4 PK samples were collected per participant at 4 different timepoints in each of the age cohorts for PK evaluation of imipenem, cilastatin, and REL. Plasma concentrations of imipenem, cilastatin, and REL and were determined using a validated high-performance liquid chromatographic tandem mass spectrometric method.

As planned, protocol-defined interim reviews of safety and PK data were completed for the participants in each age cohort to assess the suitability of the proposed initial doses. Dose modifications that were made based on the outcome of PK modelling and assessment of observed safety data as a result of the interim reviews are summarized below (Table 3.)

Table 3.

Dose Modifications After Interim Reviews
Safety Population

Cohort	Dose Regimen for IMI/REL			
	Initial	n	Modified†	n
Cohort 1	15/7.5 mg/kg over 30 min	4	500/250 mg over 30 mins	3
Cohort 2	15/7.5 mg/kg over 30 min	3	15/7.5 mg/kg over 60 min	3
Cohort 3	15/7.5 mg/kg over 30 min	3	15/7.5 mg/kg over 60 min	3
Cohort 4	10/5 mg/kg over 60 min	4	15/7.5 mg/kg over 60 min	4
Cohort 5	10/5 mg/kg over 60 min	10	15/7.5 mg/kg over 60 min	9

†Modified dosage after protocol-specified interim reviews. In Cohort 5, the initial study dose was the same across all 3 Subcohorts, and the modified study dose was the same across all 3 Subcohorts.
Cohort 1=12 to <18 years
Cohort 2=6 to <12 years
Cohort 3=2 to <6 years
Cohort 4=3 months to <2 years
Cohort 5=birth to <3 months

Source: [P020MK7655A: adam-adsl]

A total of 51 participants were screened, 47 were allocated, and 46 received study medication (a single dose of IV IMI/REL). All 46 participants who received IMI/REL completed the study as per the protocol. 42 of the 46 treated participants were included in the popPK population for the PK analyses, and 4 participants were excluded from the Per Protocol population due to protocol deviations with the dosing extended beyond the planned infusion duration.

Population PK modeling leveraging sparse PK data per participant was performed to summarize PK parameters (Systemic clearance and V1) and PK exposures ($AUC_{0-\infty}$ and C_{max}) for both imipenem and REL.

NCA was performed for cilastatin. Because of the sparse PK sampling schedule per participant, the λz NCA parameter was not calculated for the cilastatin analyte. As a result, the NCA PK parameters depending on λz, were also not calculated (including AUC0-∞, CL, and V1) for cilastatin.

Summary statistics of imipenem, REL and cilastatin PK parameters in Cohorts 1 through 5 are presented in Table 4, Table 5, and Table 6, respectively. Note that in the tables the initial dose in all cohorts are listed however the MAH states that the summary of cohort-specific PK parameters is described by actual dose administered and infusion duration.

Table 4.

Summary PK Parameters of Imipenem, Following the Administration of Single IV Dose of Imipenem/Cilastatin/Relebactam (IMI/REL) to Cohort 1-5 Participants, Presented as GM(%CV)

Cohort (Dose IMI/REL)	N	CL (L/hr/kg) [a]	CL (L/hr)	V1 (L)	Cmax (µM)	AUC0-6hr (µM*hr)	AUC0-∞ (µM*hr)	%*f* T>MIC [b]
Cohort 1 (500/250 mg -30 min Infusion)	6	0.26 (17.6)	12.58 (18.4)	10.27 (16.2)	107.6 (16.4)	131.5 (18.6)	134.7 (19.8)	56.5 (17.1)
Cohort 2 (15/7.5 mg/kg-30 min Infusion)	1	0.32 (NC)	9.60 (NC)	8.00 (NC)	126 (NC)	151.1 (NC)	153.2 (NC)	58.3 (NC)
Cohort 2 (15/7.5 mg/kg-60 min Infusion)	2	0.23 (37.2)	5.25 (9.2)	4.33 (5.2)	123 (20.6)	211.8 (36.3)	219.4 (39.2)	80.3 (26.7)
Cohort 2 (500/250 mg-30 min Infusion)	2	0.25 (7.2)	11.67 (27.6)	9.60 (2.4)	114.2 (9.2)	135.9 (24.5)	139.4 (26.6)	61.6 (25.1)
Cohort 2 (500/250 mg-60 min Infusion)	1	0.32 (NC)	11.74 (NC)	8.70 (NC)	110.6 (NC)	138.7 (NC)	140 (NC)	56.7 (NC)
Cohort 3 (15/7.5 mg/kg-30 min Infusion)	3	0.32 (17.9)	5.31 (29.7)	3.49 (19.6)	150.3 (6.7)	154.6 (18.4)	156 (18.9)	50.1 (15.7)
Cohort 3 (15/7.5 mg/kg-60 min Infusion)	3	0.31 (29.2)	4.43 (45.2)	2.49 (34.6)	125.1 (25.2)	161.4 (30.5)	163 (31.2)	57.7 (18.8)
Cohort 4 (10/5 mg/kg-60 min Infusion)	4	0.35 (40.4)	3.31 (60.1)	2.39 (53.2)	64.9 (29.6)	93.5 (37.7)	95.4 (39.3)	50.4 (30.5)
Cohort 4 (15/7.5 mg/kg-60 min Infusion)	4	0.23 (40.3)	1.70 (48.1)	1.52 (35)	127.7 (36)	213.3 (37.6)	219.2 (39.6)	73.9 (19.7)
Cohort 5 (10/5 mg/kg-60 min Infusion)	6	0.22 (15.8)	1.10 (26.2)	1.06 (29.6)	79.4 (26.4)	146.8 (15)	152.5 (14.1)	70.2 (10.6)
Cohort 5 (15/7.5 mg/kg-60 min Infusion)	9	0.19 (14.4)	0.66 (20.4)	0.95 (34.2)	119.8 (16.8)	242.8 (13.5)	271.3 (15.4)	93.7 (9.3)

NC=Not Calculated; [a] represents body weight normalized clearance; [b] represents calculation using threshold MIC value of 2 µg/mL

Source: [P020MK7655A: analysis-adpp]

Table 5.

Summary PK Parameters of MK-7655 (Relebactam), Following the Administration of Single IV Dose of Imipenem/Cilastatin/Relebactam (IMI/REL) to Cohort 1-5 Participants, Presented as GM(%CV)

Cohort (Dose IMI/REL)	N	CL (L/hr/kg) [a]	CL (L/hr)	V1 (L)	Cmax (µM)	AUC0-6hr (µM *hr) [b]	AUC0-∞ (µM*hr)
Cohort 1 (500/250 mg -30 min Infusion)	6	0.18 (15.5)	8.98 (20.7)	10.58 (17.2)	49.33(23)	74.79 (17.1)	80.1 (20)
Cohort 2 (15/7.5 mg/kg-30 min Infusion)	1	0.20 (NC)	6.10 (NC)	6.76 (NC)	86.52 (NC)	102.6 (NC)	105.6 (NC)
Cohort 2 (15/7.5 mg/kg-60 min Infusion)	2	0.17 (59.5)	3.96 (28.9)	4.95 (1.6)	60.32 (30.7)	111.8 (48.9)	123.8 (59.5)
Cohort 2 (500/250 mg-30 min Infusion)	2	0.17 (14.8)	8.03 (35.7)	9.81 (6.1)	57.44 (26.1)	84.53 (29.4)	90.3 (35.1)
Cohort 2 (500/250 mg-60 min Infusion)	1	0.23 (NC)	8.65 (NC)	9.38 (NC)	48.73 (NC)	76.58 (NC)	80.2 (NC)
Cohort 3 (15/7.5 mg/kg-30 min Infusion)	3	0.25 (30.4)	4.20 (40.8)	3.83 (13.8)	59.05 (9.08)	83.1 (30.1)	85.7 (32.4)
Cohort 3 (15/7.5 mg/kg-60 min Infusion)	3	0.26 (37.8)	3.65 (54.1)	2.88 (27.4)	48.59 (22.9)	79.23 (39.1)	81.7 (42)
Cohort 4 (10/5 mg/kg-60 min Infusion)	4	0.27 (34.8)	2.56 (54.5)	2.43 (38.8)	32.74 (15)	50.56 (31.3)	52.8 (33.6)
Cohort 4 (15/7.5 mg/kg-60 min Infusion)	4	0.17 (53.8)	1.27 (62.9)	1.70 (21.1)	59.55 (17.1)	114.00 (39.1)	126.6 (53.7)
Cohort 5 (10/5 mg/kg-60 min Infusion)	6	0.16 (17.9)	0.74 (27)	1.21 (24.6)	34.22 (17.3)	81.59 (16.4)	91.8 (18.3)
Cohort 5 (15/7.5 mg/kg-60 min Infusion)	9	0.10 (32.5)	0.35 (30.7)	0.90 (36.7)	61.04 (21.9)	158.8 (15.9)	220.7 (34.1)

NC=Not Calculated; [a] represents body weight normalized clearance; [b] represents calculation using threshold MIC value of 2 µg/mL

Source: [P020MK7655A: analysis-adpp]

Table 6.

Summary PK Parameters of Cilastatin, Following the Administration of Single IV Dose of Imipenem/Cilastatin/Relebactam (IMI/REL) to Cohort 1-5 Participants, Presented as AM(SD) and GM(%CV)

		Cilastatin								
		Ceoi (µM)		Tlast (hr)	Clast (µM)		AUClast (hr*µM)		AUC0-6hr (hr*µM)[b]	
Cohort (Dose IMI/REL)	N	AM(SD)	GM(%CV)	Median (min-max)	AM(SD)	GM(%CV)	AM(SD)	GM(%CV)	AM(SD)	GM(%CV)
Cohort 1 (Dose 15/7.5 mg/kg)	6	92.2 (32)	86.9 (41)	5.0 (4.7 - 5.5)	3.39 (4.6)	1.91 (150)	111 (45)	103 (48)		
Cohort 2 (Dose 15/7.5 mg/kg)	6	99.2 (34)	95.0 (32)	4.8 (2.1 - 5.2)	5.26 (5.3)	3.73 (110)	139 (78)	125 (54)		
Cohort 3 (Dose 15/7.5 mg/kg)	6	97.6 (37)	91.0 (45)	3.0 (1.6 - 5.2)	6.60 (4.9)	4.13 (200)	105 (61)	91.1 (65)		
Cohort 4 (Dose 10/5 mg/kg)	4	41.0 (19)[a]	37.0 (64)[a]	3.2 (1.7 - 4.9)	5.16 (4.2)	3.80 (120)	43.2 (35)	30.3 (140)		
Cohort 4 (Dose 15/7.5 mg/kg)	4	100 (41)	94.5 (42)	5.1 (4.6 - 5.3)	7.53 (11)	3.64 (230)	174 (110)	152 (63)		
Cohort 5 (Dose 10/5 mg/kg)	7	65.7 (18)	63.6 (28)	6.2 (2.6 - 6.6)	7.69 (8.3)	4.74 (150)	142 (68)	131 (44)	142 (61)	132 (39)
Cohort 5 (Dose 15/7.5 mg/kg)	9	109 (21)	107 (20)	6.5 (2.8 - 12)	23.0 (15)	18.5 (92)	368 (150)	342 (42)	352 (90)	342 (26)

N: Number of participants; AM: Arithmetic Mean; SD: Standard deviation; GM: Geometric Mean; %CV: Coefficient of variation; min: minimum; max: maximum;
Ceoi: Concentration at end of infusion (30 min for cohort 1, 60 min for cohort 2 to 5); AUC0-6h: AUC from time of dosing to time 6 hours;
a: N = 3 due to an outlier; b: For cohort 1-4, AUC0-6hr could not be determined because of the limited sampling scheme (no half life could be calculated) and no sample taken after 6 hr.

Source: [P020MK7655A: analysis-adpp]

Efficacy results

Study P020 was a single-dose PK and safety study and clinical efficacy was not evaluated.

Safety results

Safety analyses were based on the safety population, which included all 46 allocated participants who received infusion of study medication.

Table 7. Extent of Exposure – Safety Population

IMI/REL	n	Actual Mean Dose	Actual Median Dose	Actual Median Duration	Actual Mean Duration	Actual Duration Range
Cohort 1 (15/7.5 mg/kg; 30 min)	7	500.0 mg	500.0 mg	30 mins	36.6 mins	28 to 80 mins
Cohort 2 (15/7.5 mg/kg; 30 min)	3	483.3 mg	500.0 mg	30 mins	29.3 mins	28 to 30 mins
Cohort 2 (15/7.5 mg/kg; 60 min)	3	399.2 mg	414.0 mg	60 mins	60.0 mins	60 to 60 mins
Cohort 3 (15/7.5 mg/kg; 30 min)	3	251.5 mg	252.0 mg	30 mins	30.0 mins	30 to 30 mins
Cohort 3 (15/7.5 mg/kg; 60 min)	3	213.0 mg	219.0 mg	60 mins	60.0 mins	60 to 60 mins
Cohort 4 (10/5 mg/kg; 60 min)	4	96.8 mg	98.5 mg	60 mins	60.0 mins	60 to 60 mins
Cohort 4 (15/7.5 mg/kg; 60 min)	4	112.9 mg	111.3 mg	60 mins	60.0 mins	60 to 60 mins
Cohort 5 (10/5 mg/kg; 60 min)	10	44.5 mg	40.0 mg	61 mins	63.2 mins	60 to 74 mins
Cohort 5 (15/7.5 mg/kg; 60 min)	9	53.9 mg	54.0 mg	60 mins	60.2 mins	60 to 62 mins

Treatment duration = the number of minutes between the start and end of IV therapy.
Each subject is counted once on each applicable dosage category row.
All subjects received a single intravenous dose of a fixed-dose combination of imipenem/cilastatin/relebactam, hereafter referred to as IMI/REL. Dosage were modified after each interim review.
The maximum allowable dose across all cohorts was equivalent to the adult dose of 500 mg IMI and 250 mg REL.
The initial dose for Cohort 1 is 15/7.5 mg/kg prior to interim review, all subjects received the full adult dose of 500/250 mg IMI/REL based on their weight. Therefore, the dose was modified to 500/250 mg after the interim review.
Cohort 1=12 to <18 years
Cohort 2=6 to <12 years
Cohort 3=2 to <6 years
Cohort 4=3 months to <2 years
Cohort 5=birth to <3 months

Source: CLINICAL STUDY REPORT P020MK7655A Table 10-6.

Safety results are summarized overall and then separately for different age group cohorts in the submitted report, as significant physiological differences exist for paediatric patients of different age groups (eg, older age Cohorts 1-3 [2 to <18 years] vs those enrolled in younger age Cohorts 4-5 [<2 years]).

Overall, for Cohorts 1-5, 8 participants (17.4%) experienced at least 1 AE and 2 participants (4.3%) had AEs categorized as drug-related by the investigator. All reported AEs occurred in the post-treatment period, most were mild in severity, none were SAEs or fatal events, and none led to infusion interruption/discontinuation or study discontinuation. Overall, for Cohorts 1-5, the most frequently reported AEs were anaemia (6.5%), and diarrhoea (6.5%). Drug-related AEs reported in the study were increased ALT, increased AST, anaemia, and diarrhoea.

Elevations in liver transaminases meeting pre-defined criteria were categorized as Adverse Events of Special Interest. No events meeting these criteria were documented.

Thirty-eight participants (3 in Cohort 1, 5 in Cohort 2, 6 in Cohort 3, 8 in Cohort 4 and 16 in Cohort 5) had at least one laboratory value at post-treatment Visit 3 that met DMID or DAIDS toxicity (for

calcium results) grades of 1-4 (majority were Grade 1 or 2). No clinically meaningful changes in chemistry and haematology mean values or vital signs were observed in any of the cohorts from Baseline to Visit 3.

2.3.3. Discussion on clinical aspects

Relebactam (REL) is a non-β-lactam BLI of the diazobicyclooctane family and an inhibitor of Ambler class A and class C β-lactamases. REL restores the activity of imipenem in carbapenem-resistant gram-negative bacterial infections. REL has been developed for administration as an FDC with imipenem and cilastatin in a single vial, for IV administration (IMI/REL).

IMI/REL was initially approved in the EU in February 2020 for the treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options. Subsequently, in November 2020, IMI/REL was approved by the European Commission for the additional indication for treatment of HAP, including VAP, in adults and bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP, in adults.

Study P020 was conducted in accordance with guidance from the EMA-CHMP and US FDA and is part of the PIP approved by the EMA (PIP EMEA-001809-PIP01-15-M02). The information from this Phase 1b study will be used to determine appropriate dosing regimens for a Phase 2/3 efficacy study of IMI/REL in the paediatric population (Study P021). A variation applicant comprising data to support the efficacy, safety, and PK of IMI/REL to treat paediatric patients with HAP, including VAP, and bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP, and infections due to aerobic gram-negative organisms with limited treatment options, is expected by end of 2023.

P020 was an open-label, noncomparative Phase 1b study of a single IV dose of IMI/REL in male and female paediatric participants receiving standard-of-care antibacterial therapy for treatment of a confirmed or suspected gram-negative bacterial infection. Study P020 was a single-dose PK and safety study and clinical efficacy was not evaluated.

Interim PK analysis resulted in modified doses for Cohort 1 (12 to <18), 4 (3 months to <2 years) and 5 (birth to <3 months) (Table 3).

In general, treatment with a single dose of IMI/REL was generally well tolerated and AEs occurred with low frequency. Eight participants (17.4%) experienced at least 1 AE in the study, of which 2 participants (4.3%) experienced mild AEs categorized as drug-related by the investigator (increased ALT, increased AST, anaemia in 1 participant; diarrhoea in 1 participant). All AEs were reported in the post-treatment period and therefore did not result in infusion interruption/discontinuation or study discontinuation. No SAEs or deaths were reported during the study. These results are in keeping with the known safety profile of IMI/REL in adults and the underlying clinical condition being treated.

3. Rapporteur's overall conclusion and recommendation

The results of this study indicate that a single dose of IMI/REL IV infusion was generally well tolerated in paediatric participants (from birth to less than 18 years of age). No safety concerns were observed during the study.

The results of this study do not impact or alter the overall benefit/risk balance of IMI/REL in the currently authorised indications and populations and do not warrant any changes to the terms of marketing authorisation or updates to the Product Information at this time.

The submitted study is part of a paediatric clinical development program. The variation application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by end of 2023.

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

Product Name: Recarbrio
Active substance: relebactam monohydrate, cilastatin sodium, relebactam, cilastatin, imipenem monohydrate, imipenem (anhydrous)

Non-clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
Dose range-finding juvenile toxicity study	(PIP study 1)	2 December 2015	8 November 2018
Definitive juvenile toxicity study	(PIP study 2)	19 October 2016	8 November 2018

Clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
Phase 1b, noncomparative, open-label, single IV dose study to evaluate the PK, safety, and tolerability of imipenem/cilastatin/relebactam in paediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative infections.	P020 (PIP study 3)	11-Aug-2020	04-Feb-2021
Open-label, randomised, active-controlled trial to evaluate safety, tolerability and efficacy of MK-7655A in children from birth to less than 18 years of age with gram-negative bacterial infections.	*P021* *(PIP study 4)*		

Other studies

Study title	Study number	Date of completion	Date of submission of final study report

Population PK modelling and PK/PD probability of target attainment (PTA) analysis using step-down approach to select doses for the paediatric age range from birth to less than 18 years of age.	*(PIP study 6)*		
Extrapolation study of efficacy data for MK-7655A from the adult Phase II and III programme to paediatric patients with HABP/VABP pneumonia or with serious infections (HABP/VABP, cIAI or cUTI) caused by carbapenem-resistant (CR) gram-negative bacteria.	*(PIP study 7)*		