30 January 2025
EMA/70482/2025
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/P46/005

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**	**Need for discussion**
☐	Start of procedure	02 Dec 2024	02 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	06 Jan 2025	27 Dec 2024	☐
☐	CHMP members comments	20 Jan 2025	20 Jan 2025	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	22 Jan 2025	☐
☒	CHMP adoption of conclusions:	30 Jan 2025	30 Jan 2025	☐

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1. Introduction

On 18 October 2024, the MAH submitted a completed paediatric study for Recarbrio, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study "A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Pediatric Participants from Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection", P021MK7655A, also called MK-7655A-021, PN021, Ped002, and P021) is part of the paediatric clinical development programme for Recarbrio. A variation application consisting of the full relevant data package (i.e containing several studies) to support the extension of indication(s) from adults to children is expected to be submitted by 06/25. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Treatment was given with imipenem-cilastatin-relebactam (IMI/REL) powder for suspension, with an option for oral switch to an appropriate oral antibacterial agent.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- P021MK7655A, A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Pediatric Participants from Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection.

2.3.2. Clinical study

P021MK7655A, A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Pediatric Participants from Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection.

Description

The study was a Phase 2/3 randomized, active-controlled, parallel-group, multi-site, open-label study of IMI/REL in paediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative bacterial infections. Participants with HAP/VAP, cIAI, or cUTI were randomized in a 3:1 ratio to receive IMI/REL or active control. Participants were stratified by age group and infection type prior to randomization.

Five paediatric age cohorts were to be evaluated in the study:

- Age Cohort 1: Adolescents (12 to <18 years)

- Age Cohort 2: Older Children (6 to <12 years)
- Age Cohort 3: Younger Children (2 to <6 years)
- Age Cohort 4: Infants and Toddlers (3 months to <2 years)
- Age Cohort 5: Neonates and Young Infants (birth to <3 months)

Methods

Safety, tolerability, efficacy, and PK were assessed during the intervention and follow-up periods. Study visits were performed at randomization (Day 1), on therapy (OTX), at the end of IV therapy (EOIV, only for participants who switch to oral therapy), and at the end of therapy (EOT). Following the completion of all study intervention, participants were evaluated 7 to 14 days after EOT (at the Early Follow-up [EFU] visit) and 7 to 14 days after the EFU visit (at the Late Follow-up [LFU] visit). The investigator was allowed to switch participants with cIAI or cUTI to oral antibacterial therapy based on the participant's clinical condition after a minimum of 3 days of IV study intervention; these participants had an EOIV visit and completed a minimum of 5 days up to a maximum of 14 days of all study intervention (IV + oral). Oral switch was not allowed for participants with HAP/VAP, and completed a minimum of 7 days of IV study intervention. Safety and tolerability was monitored periodically throughout the study and at the planned interim analysis by an eDMC in conjunction with the Sponsor Executive Oversight Committee (EOC).

Age Cohorts 1, 2, and 3, were enrolled in parallel. To assess whether the safety and tolerability profile was acceptable overall and for each age cohort and to confirm the proposed initial doses for Age Cohorts 4 and 5, an interim analysis was performed when at least 30 participants in each of Cohorts 1, 2, and 3 had final data available. Once the proposed initial doses for Age Cohorts 4 and 5 were confirmed based on the findings from the interim analysis, enrolment in Age Cohorts 4 and 5 was done in parallel.

Study participants

Male or female participants from birth to less than 18 years of age who required hospitalization and treatment with IV antibacterial therapy for confirmed or suspected Gram-negative bacterial infection (in the absence of meningitis) involving 1 of 3 primary infection types: HAP/VAP, cUTI, or cIAI.

Treatments

Treatment details are given in the table below. Briefly, active treatment was IMI/REL given as intravenous infusion at doses 15/7.5 mg/kg q6-8h or 500/250 mg q6h, based on cohort. Active control was given per investigators discretion from a list of predefined treatments, dosed according to approved product information or international guidelines.

An option for oral switch was allowed for patients with cIAI or cUTI after at least 3 days of i.v. therapy, based on clinical condition.

Arm Name	Arm Type	Interven-tion Name	Interven-tion Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s) IMI/REL	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
IMI/ REL	Experiment-al	IMI/REL	Drug	Powder, For Suspension	relebactam, imipenem, cilastatin 250/500/500 mg	Age Cohort 1: 500/250 mg q6h Age Cohort 2: 15/7.5 mg/kg q6h Age Cohort 3: 15/7.5 mg/kg q6h Age Cohort 4: 15/7.5 mg/kg q6h Age Cohort 5: 15/7.5 mg/kg q8h All administered as 60-minute infusions	IV Infusion	cIAI and cUTI: Total duration of all study intervention: Minimum 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days; HABP/VABP: Minimum 7 days up to a maximum of 14 days.	Test Product	IMP	Sponsor

Arm Name	Arm Type	Interven-tion Name	Interven-tion Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s) IMI/REL	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Active Control	Active Comparator	Acceptable control options for each infection type	Drug	Powder, For Suspension	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	IV Infusion	cIAI and cUTI: Total duration of all study intervention: Minimum 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days; HABP/ VABP: Minimum 7 days up to a maximum of 14 days. All administered per authorized PI, SPC, or international treatment guidelines.	Comparator	IMP	Locally

Arm Name	Arm Type	Interven-tion Name	Interven-tion Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s) IMI/REL	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
IMI/ REL	Experimental	Acceptable oral switch options for cIAI and cUTI	Drug	Liquid	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	Oral	Per authorized PI, SPC, or international treatment guidelines	Systemically Prescribed	IMP	Locally
Active Control	Active Comparator	Acceptable oral switch options for cIAI and cUTI	Drug	Liquid	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	Oral	Per authorized PI, SPC, or international treatment guidelines	Systemically Prescribed	IMP	Locally

cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EDC=electronic data collection; EEA=European Economic Area; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; IMI/REL= imipenem/cilastatin/relebactam (MK-7655A); IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PI=Package Insert; PO=per oral (by mouth); q6h=every 6 hours; q8h=every 8 hours; SPC=Summary of Product Characteristics.

Note: The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note: Protocol-allowed comparator medications for each infection type are detailed by generic drug name in the EDC system, EDC guidelines, and Appendix 9 of the protocol [16.1.1].

Note: Study intervention, dose, and regimen are listed by infection type in Table 2 of the protocol [16.1.1].

Source: Table 1 of the protocol [16.1.1].

Predefined active control treatments were:

- HAP/VAP: i.v. carbapenem, i.v. piperacillin/tazobactam, or i.v. cefepime.
- cIAI: i.v. carbapenem or i.v. 3rd generation cephalosporin + metronidazole, with oral switch to p.o. β-lactam/inhibitor, p.o. 2nd or 3rd generation cephalosporin + metronidazole, or p.o. quinolone +/- metronidazole.
- cUTI: i.v. 3rd or 4th generation cephalosporin, or i.v. ciprofloxacin, with oral switch to p.o. β-lactam/inhibitor, p.o. cephalosporin, p.o. nitrofurantoin, or p.o. trimethoprim +/- sulfamethoxazole.

Objectives

Primary Objective	Primary Endpoint
To evaluate the safety and tolerability of IMI/REL (imipenem/cilastatin/relebactam) from the first dose of intravenous (IV) study intervention through 14 days after the end of therapy (EOT)	Adverse events (AEs) IV study intervention discontinuations due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of IMI/REL by assessing all-cause mortality at Day 28 post-randomization and clinical and microbiological response at the EOT, Early Follow-up (EFU, 7 to 14 days after EOT), and Late Follow-up (LFU, 7 to 14 days after EFU) visits	All-cause mortality Favorable clinical response Favorable microbiological response
To characterize the PK profile of imipenem and relebactam following administration of IMI/REL	Plasma concentrations of imipenem and relebactam $AUC_{0\text{-}24hr}$ and C_{eoi} for imipenem and relebactam %*f*T>MIC for imipenem
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the efficacy of IMI/REL by assessing clinical and microbiological response at the End of IV (EOIV) visit (for participants who switch to oral therapy) To evaluate the efficacy of IMI/REL by assessing by-pathogen microbiological response at the EOIV (for participants who switch to oral therapy), EOT, EFU, and LFU visits	Favorable clinical response Favorable microbiological response Favorable by-pathogen microbiological response

Outcomes/endpoints

See table above.

Sample size

Approximately 140 participants were planned to be randomized in a 3:1 ratio to receive IMI/REL or active control. As differences in the distribution of infection types within each age cohort were considered likely, a balance of infection types across age cohorts was unlikely to be achievable; therefore, an interactive response technology (IRT) system was be used to meet the following targets:

- Minimum of 28 participants each Approximately 50 participants each with HAP/VAP and cIAI enrolled.
- At least 10% of participants with cIAI have a diagnosis other than complicated appendicitis.
- A maximum of 48 with cUTI in the 3 youngest Age Cohorts (3, 4, and 5) combined, but no minimum.

Randomisation and blinding (masking)

A 3:1 randomisation ratio was selected to gain greater experience with IMI/REL and to maximize the opportunity to assess safety and efficacy. Randomization was stratified by age and by infection type for balanced distribution across age cohorts and infection types. The oldest 3 age cohorts (Age Cohorts 1, 2, and 3) were studied in parallel. Enrolment in the 2 youngest age cohorts (Age Cohorts 4 and 5) was initiated after completion of the interim review of aggregated safety, tolerability, efficacy, and PK data from Age Cohorts 1, 2, and 3, and confirmation of doses.

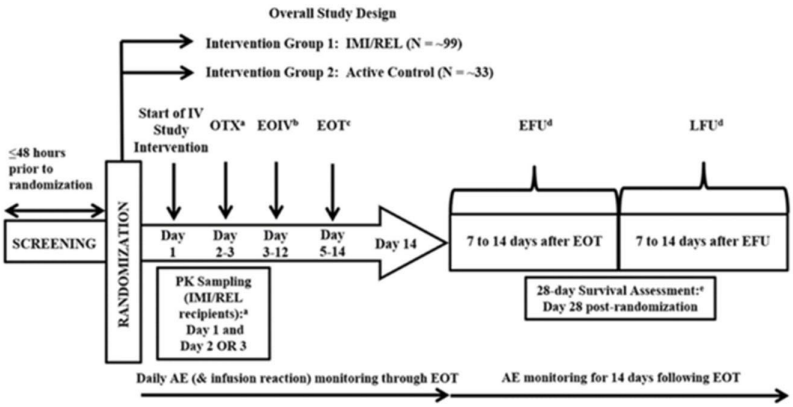
The study was open-label; therefore, the Sponsor, investigator, and participant know which intervention was administered.

Statistical Methods

No hypothesis testing was performed, rather, point estimates of efficacy and safety endpoints were calculated with within-group and between-group confidence intervals. PK data were used to update the paediatric popPK model.

Results

Participant flow



Recruitment

The disposition of all randomized participants was generally comparable for the IMI/REL and Active Control intervention groups [Table 10-1]. Disposition across age cohorts was generally comparable, although the interpretation of differences in disposition across age cohorts is limited by the low sample sizes (especially in the Active Control group).

A total of 130 participants were screened across 38 study sites in 18 countries. Of these, 115 participants in 35 study sites in 15 countries were randomized to treatment. All but 2 participants (1 in each treatment group) received at least 1 dose of study intervention and the majority (>82%) completed study intervention. Most participants in each age cohort completed the study and the study medication. The most common reasons for discontinuing study intervention were "other" in the IMI/REL group (7.1%) and "adverse event" and "physician decision" (each 7.1%) in the Active Control group. Most randomized participants (>96%) completed the study. The disposition of all randomized participants by infection type was generally comparable for both intervention groups. A higher percentage of participants with HAP/VAP (100%) and cIAI (92.5%) infections completed the study medication compared with participants with cUTI (74.1%).

Disposition of Participants
All Participants Randomized

	Age Cohort 1 (12 to <18 years)				Age Cohort 2 (6 to <12 years)				Age Cohort 3 (2 to <6 years)			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Participants in population	10		2		31		11		22		8	
Status for Trial												
Completed	10	(100.0)	2	(100.0)	31	(100.0)	11	(100.0)	21	(95.5)	8	(100.0)
Discontinued	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	0	(0.0)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	0	(0.0)
Status for Study Medication in Trial												
Started	10		2		31		11		21		8	
Completed	9	(90.0)	1	(50.0)	27	(87.1)	9	(81.8)	19	(90.5)	7	(87.5)
Discontinued	1	(10.0)	1	(50.0)	4	(12.9)	2	(18.2)	2	(9.5)	1	(12.5)
Adverse Event	0	(0.0)	0	(0.0)	3	(9.7)	1	(9.1)	0	(0.0)	0	(0.0)
Physician Decision	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(12.5)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Other[a]	1	(10.0)	0	(0.0)	1	(3.2)	1	(9.1)	1	(4.8)	0	(0.0)

	Age Cohort 4 (3 months to <2 years)				Age Cohort 5 (Birth to <3 months)				Total			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Participants in population	15		5		8		3		86		29	
Status for Trial												
Completed	15	(100.0)	4	(80.0)	7	(87.5)	3	(100.0)	84	(97.7)	28	(96.6)
Discontinued	0	(0.0)	1	(20.0)	1	(12.5)	0	(0.0)	2	(2.3)	1	(3.4)
Withdrawal By Parent/Guardian	0	(0.0)	1	(20.0)	1	(12.5)	0	(0.0)	2	(2.3)	1	(3.4)
Status for Study Medication in Trial												
Started	15		4		8		3		85		28	
Completed	11	(73.3)	3	(75.0)	6	(75.0)	3	(100.0)	72	(84.7)	23	(82.1)
Discontinued	4	(26.7)	1	(25.0)	2	(25.0)	0	(0.0)	13	(15.3)	5	(17.9)
Adverse Event	1	(6.7)	1	(25.0)	0	(0.0)	0	(0.0)	4	(4.7)	2	(7.1)
Physician Decision	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	2	(7.1)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	1	(1.2)	0	(0.0)
Other[a]	2	(13.3)	0	(0.0)	1	(12.5)	0	(0.0)	6	(7.1)	1	(3.6)

[a] Includes participants with extenuating circumstances (eg., microbiological criteria not met, receipt of prohibited non-study antibiotics).
Each Participant is counted once for Status for Trial, Status for Study Medication in Trial based on the latest corresponding disposition record.
The % is based on the number of participants in the population.

Source: [P021MK7655A: adam-adsl]

Baseline data

Demographic and baseline characteristics were generally comparable for both interventions except for the proportion of participants of "Not Hispanic or Latino" ethnicity which was lower in the IMI/REL group (58.1%) compared with the Active Control group (69.0%). Most participants were White, and not Hispanic or Latino; cIAI and cUTI were more common types of infection than HAP/VAP. Most participants with cIAI (39 of 40 participants) were in Age Cohorts 1, 2, and 3, whereas participants with HAP/VAP or cUTI infections were more evenly distributed across age cohorts.

Participant Characteristics by Age Cohort
All Participants Randomized

	Age Cohort 1 (12 to <18 years)				Age Cohort 2 (6 to <12 years)				Age Cohort 3 (2 to <6 years)			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Participants in population	10		2		31		11		22		8	
Sex												
Male	2	(20.0)	1	(50.0)	18	(58.1)	3	(27.3)	10	(45.5)	5	(62.5)
Female	8	(80.0)	1	(50.0)	13	(41.9)	8	(72.7)	12	(54.5)	3	(37.5)
Race												
American Indian Or Alaska Native	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	1	(12.5)
Asian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Black Or African American	0	(0.0)	0	(0.0)	2	(6.5)	1	(9.1)	0	(0.0)	0	(0.0)
Multiple	3	(30.0)	1	(50.0)	2	(6.5)	0	(0.0)	2	(9.1)	2	(25.0)
American Indian Or Alaska Native, White	3	(30.0)	1	(50.0)	2	(6.5)	0	(0.0)	1	(4.5)	1	(12.5)
Black Or African American, White	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	1	(12.5)
White	7	(70.0)	1	(50.0)	27	(87.1)	10	(90.9)	19	(86.4)	4	(50.0)
Ethnicity												
Hispanic Or Latino	5	(50.0)	1	(50.0)	9	(29.0)	1	(9.1)	12	(54.5)	4	(50.0)
Not Hispanic Or Latino	5	(50.0)	1	(50.0)	21	(67.7)	10	(90.9)	10	(45.5)	4	(50.0)
Not Reported	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)

	Age Cohort 1 (12 to <18 years)				Age Cohort 2 (6 to <12 years)				Age Cohort 3 (2 to <6 years)			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Infection Type												
cIAI	5	(50.0)	1	(50.0)	21	(67.7)	7	(63.6)	14	(63.6)	5	(62.5)
cUTI	4	(40.0)	1	(50.0)	10	(32.3)	4	(36.4)	6	(27.3)	2	(25.0)
HABP/VABP	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.1)	1	(12.5)

	Age Cohort 4 (3 months to <2 years)				Age Cohort 5 (Birth to <3 months)				Total			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Participants in population	15		5		8		3		86		29	
Sex												
Male	8	(53.3)	4	(80.0)	5	(62.5)	3	(100.0)	43	(50.0)	16	(55.2)
Female	7	(46.7)	1	(20.0)	3	(37.5)	0	(0.0)	43	(50.0)	13	(44.8)
Race												
American Indian Or Alaska Native	2	(13.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.5)	1	(3.4)
Asian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.4)
Black Or African American	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.5)	1	(3.4)
Multiple	1	(6.7)	0	(0.0)	0	(0.0)	1	(33.3)	8	(9.3)	4	(13.8)
American Indian Or Alaska Native, White	1	(6.7)	0	(0.0)	0	(0.0)	1	(33.3)	7	(8.1)	3	(10.3)
Black Or African American, White	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(3.4)
White	11	(73.3)	5	(100.0)	8	(100.0)	2	(66.7)	72	(83.7)	22	(75.9)
Ethnicity												
Hispanic Or Latino	5	(33.3)	1	(20.0)	3	(37.5)	2	(66.7)	34	(39.5)	9	(31.0)
Not Hispanic Or Latino	9	(60.0)	4	(80.0)	5	(62.5)	1	(33.3)	50	(58.1)	20	(69.0)
Not Reported	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.3)	0	(0.0)

	Age Cohort 4 (3 months to <2 years)				Age Cohort 5 (Birth to <3 months)				Total			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Infection Type												
cIAI	0	(0.0)	1	(20.0)	0	(0.0)	0	(0.0)	40	(46.5)	14	(48.3)
cUTI	14	(93.3)	4	(80.0)	7	(87.5)	3	(100.0)	41	(47.7)	14	(48.3)
HABP/VABP	1	(6.7)	0	(0.0)	1	(12.5)	0	(0.0)	5	(5.8)	1	(3.4)

cIAI = Complicated Intra-Abdominal Infection; cUTI = Complicated Urinary Tract Infection; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia.

Source: [P021MK7655A: adam-adsl]

Number analysed

The efficacy analyses were based on the MITT and mMITT populations.

Of the 115 randomized participants, 113 (98.3%) were included in the MITT population. Two randomized participants were not included in the MITT population due to withdrawal by parent/guardian.

The MITT population was used for analysis of clinical response and mMITT for analysis of microbiological response in this study. The mMITT population included all randomized participants who met the following conditions: For participants with HAP/VAP and cIAI:

- The participant received at least 1 dose of IV study intervention; AND
- The participant's baseline infection-site culture grew at least 1 Gram-negative pathogen.

For participants with cUTI:

- The participant received at least 1 dose of IV study intervention; AND
- The participant's baseline urine culture grew at least 1 Gram-negative pathogen at sufficient quantity (ie, growth at $\geq 10^5$ CFU/mL of uropathogen)

For analyses of efficacy data using the mMITT population, participants were included in the intervention group to which they were randomized.

Of the 115 randomized participants, 90 (78.3%) were included in the mMITT population. Twenty-three randomized participants (20.0%) had a baseline culture that did not meet culture identification requirements for inclusion.

Safety Analysis Population

Safety analyses were based on the APaT population, which included all randomized participants who received at least 1 dose of IV study intervention. For analyses of safety data using the APaT population, participants were included in the intervention group corresponding to the study intervention they actually received.

For this study, the APaT and MITT populations were the same. Of the 115 randomized participants, 113 (98.3%) were included in the APaT population. Two randomized participants were not included in the APaT population due to withdrawal by parent/guardian.

PK Analysis Population

PK analyses for the plasma concentration listing provided in the CSR were based on the 85 participants who received at least 1 dose of IMI/REL and had at least 1 measurable PK sample.

The other secondary PK endpoints, based on the protocol-defined PK population, will be presented in a separate paediatric population PK modelling and simulation report.

Efficacy results

All-cause Mortality Through Day 28 (MITT)

No participants died in either intervention group in the study through Day 28.

Clinical Response (MITT and mMITT)

The majority of participants in the MITT population (>69% in both intervention groups) achieved a favourable clinical response at the EOT visit (cure, improved), and favourable clinical response at the EFU and LFU visits (sustained cure, cure).

The percentage of participants with a favourable clinical response at the EOT, EFU, and LFU visit was numerically comparable for the IMI/REL and Active Control groups.

Results for favourable clinical responses by outcome categories and by visit were generally comparable for both intervention groups.

Analysis of Clinical Response by Visit – All Infection Types
Modified Intent-To-Treat Population

	IMI/REL			Active Control			Difference in % vs Active Control	
	n	%	(95% CI)[c]	n	%	(95% CI)[c]	%	(95% CI)[d]
Participants in population	85			28				
EOT								
Favorable[a]	67	78.8	(68.9, 86.2)	21	75.0	(56.4, 87.6)	3.8	(-12.3, 23.9)
Cure	57	67.1		20	71.4			
Improvement	10	11.8		1	3.6			
Unfavorable	18	21.2		7	25.0			
Failure	1	1.2		0	0.0			
Indeterminate[e]	17	20.0		7	25.0			
EFU								
Favorable[b]	60	70.6	(60.1, 79.3)	21	75.0	(56.4, 87.6)	-4.4	(-21.1, 16.1)
Sustained cure	53	62.4		20	71.4			
Cure	7	8.2		1	3.6			
Unfavorable	25	29.4		7	25.0			
Relapse	4	4.7		0	0.0			
Failure	1	1.2		0	0.0			
Indeterminate[e]	20	23.5		7	25.0			
LFU								
Favorable[b]	59	69.4	(58.9, 78.2)	21	75.0	(56.4, 87.6)	-5.6	(-22.3, 15.0)
Sustained cure	57	67.1		21	75.0			
Cure	2	2.4		0	0.0			
Unfavorable	26	30.6		7	25.0			
Relapse	4	4.7		0	0.0			
Failure	1	1.2		0	0.0			
Indeterminate[e]	21	24.7		7	25.0			

EOT = end of therapy; EFU = early follow-up; LFU = late follow-up.
[a] A favorable clinical response at EOT requires an assessment of "cure" or "improved".
[b] A favorable clinical response at EFU or LFU requires an assessment of "cure" or "sustained cure". To be considered "sustained cure", the clinical response for the prior visit (EOT or EFU) must have been considered "cure".
[c] 95% confidence intervals are based on Agresti & Coull method.
[d] 95% confidence intervals are based on unstratified Miettinen & Nurminen method.
[e] Study data were not available for evaluation of the clinical response for any reason at the visit, including withdrawal of consent or extenuating circumstances (e.g., discontinuation of study medication, microbiological criteria not met, receipt of prohibited non-study antibiotics, new infection, or superinfection).
The % is based on the number of participants in the population.

The majority of participants in the mMITT population (>79%, in both intervention groups) achieved a favourable clinical response at the EOT, EFU, and LFU visits. The percentage of participants with a favourable clinical response at the EOT, EFU, and LFU visits was comparable for both intervention groups (the 95% CIs of the difference in percentage for IMI/REL vs Active Control groups included 0).

Results for favourable clinical responses by outcome categories and by visit were generally comparable for both intervention groups.

Clinical Response by Age Cohort and Infection Type (MITT, mMITT)

The percentage of participants with a favourable clinical response at the EOT, EFU, and LFU visits was generally comparable for both intervention groups, overall and across age cohorts, within each infection type.

The percentage of participants with cUTI with a favourable clinical response at the EOT, EFU, and LFU visits was in general numerically lower than rates for cIAI for both intervention groups.

In the MITT population, a higher percentage of participants with cUTI was reported with a clinical response category of "indeterminate" compared with participants with HAP/VAP and cIAI for both intervention groups. Participants with indeterminate outcomes included those who failed to meet microbiological criteria in this response category and those who received prohibited antibiotic treatment.

Microbiological Response (mMITT)

Most participants in the mMITT population (>85% in both intervention groups) achieved a favourable microbiological response at the EOT, EFU, and LFU visits (eradication, presumed eradication). The percentage of participants with a favourable microbiological response at the EOT, EFU, and LFU visit was numerically comparable for the IMI/REL and Active Control groups. Results for favourable microbiological responses by outcome categories and by visit were generally comparable for both intervention groups.

Table 11-3
Analysis of Overall Microbiological Response by Visit – All Infection Types
Microbiological Modified Intent-To-Treat Population

	IMI/REL			Active Control			Difference in % vs Active Control	
	n	%	(95% CI)[a]	n	%	(95% CI)[a]	%	(95% CI)[b]
Participants in population	68			22				
EOT								
Favorable	65	95.6	(87.3, 99.0)	20	90.9	(71.0, 98.7)	4.7	(-5.6, 23.9)
Unfavorable	3	4.4		2	9.1			
Indeterminate	3	4.4		2	9.1			
EFU								
Favorable	58	85.3	(74.8, 92.0)	20	90.9	(71.0, 98.7)	-5.6	(-18.5, 14.4)
Unfavorable	10	14.7		2	9.1			
Indeterminate	5	7.4		2	9.1			
LFU								
Favorable	59	86.8	(76.5, 93.1)	19	86.4	(65.8, 96.1)	0.4	(-13.5, 21.3)
Unfavorable	9	13.2		3	13.6			
Indeterminate	6	8.8		2	9.1			

EOT = end of therapy; EFU = early follow-up; LFU = late follow-up.
[a] 95% confidence intervals are based on Agresti & Coull method.
[b] 95% confidence intervals are based on unstratified Miettinen & Nurminen method.
For participants from whom only 1 pathogen is isolated in the baseline infection-site culture, the microbiological response assessment will be based on the microbiological response rating for that pathogen. For participants from whom more than 1 baseline pathogen is isolated in the baseline infection-site culture, the microbiological response outcome will be based on microbiological culture results for all pathogens (ie, a "favorable" overall microbiological response requires eradication or presumed eradication of all baseline pathogens).
The % is based on the number of participants in the population.

Source: [P021MK7655A: adam-adsl; adeff]

Microbiological Response by Age Cohort and Infection Type (mMITT)

The percentage of participants in the mMITT population with a favourable microbiological response at the EOT, EFU, and LFU visits was generally comparable for both intervention groups, overall and across age cohorts, within each infection type.

The percentage of participants with cUTI infection type with a favourable microbiological response at the EOT, EFU, and LFU visits was in general lower than for the percentage of participants with cIAI for both intervention groups.

Safety results

Adverse Events

Overall, 57 (67.1%) participants receiving IMI/REL experienced at least 1 AE; most of these were not considered by the investigator to be related to study intervention. Most AEs were mild or moderate in intensity and generally comparable for both intervention groups.

The percentage of participants who had any drug-related AE, SAE, and AE leading to discontinuation was comparable for both intervention groups. There were no AEs reported with an outcome of death or SAEs leading to discontinuations of IV study intervention. There were few participants (≤ 3) who had drug-related SAEs, AEs leading to discontinuations of IV study intervention, or discontinuations due to drug-related AEs.

Analysis of Adverse Events Summary During Therapy and 14-Day Follow-up Period
All Participants as Treated

	IMI/REL		Active Control		Difference in % vs Active Control
	n	(%)	n	(%)	Estimate (95% CI)[c]
Participants in population	85		28		
with one or more adverse events	57	(67.1)	14	(50.0)	17.1 (-3.5, 37.2)
with no adverse event	28	(32.9)	14	(50.0)	-17.1 (-37.2, 3.5)
with drug-related[a] adverse events	17	(20.0)	5	(17.9)	2.1 (-17.2, 16.6)
from IV therapy	16	(18.8)	5	(17.9)	1.0 (-18.3, 15.3)
from oral step-down therapy	1	(1.2)	0	(0.0)	1.2
with serious adverse events	10	(11.8)	3	(10.7)	1.1 (-16.4, 12.5)
with serious drug-related[a] adverse events	2	(2.4)	0	(0.0)	2.4
from IV therapy	1	(1.2)	0	(0.0)	1.2
from oral step-down therapy	1	(1.2)	0	(0.0)	1.2
who died	0	(0.0)	0	(0.0)	0.0
discontinued drug due to an adverse event[d]	5	(5.9)	2	(7.1)	-1.3 (-17.3, 7.8)
discontinued IV therapy[b]	3	(3.5)	0	(0.0)	3.5
discontinued oral step-down therapy	2	(2.4)	2	(7.1)	-4.8 (-20.6, 2.8)
discontinued drug due to a drug-related adverse event[d]	3	(3.5)	0	(0.0)	3.5
discontinued IV therapy[b]	2	(2.4)	0	(0.0)	2.4
discontinued oral step-down therapy	1	(1.2)	0	(0.0)	1.2
discontinued drug due to a serious adverse event[d]	2	(2.4)	2	(7.1)	-4.8 (-20.6, 2.8)
discontinued IV therapy[b]	0	(0.0)	0	(0.0)	0.0
discontinued oral step-down therapy	2	(2.4)	2	(7.1)	-4.8 (-20.6, 2.8)
discontinued drug due to a serious drug-related adverse event[d]	1	(1.2)	0	(0.0)	1.2
discontinued IV therapy[b]	0	(0.0)	0	(0.0)	0.0
discontinued oral step-down therapy	1	(1.2)	0	(0.0)	1.2

[a] Determined by the investigator to be related to the drug.
[b] IV study medication withdrawn during IV treatment phase.
[c] Based on Miettinen & Nurminen method, and presented if incidence ≥12 participants in the IMI/REL group or ≥2 participants in the Active Control group.
[d] One participant in the IMI/REL arm discontinued oral step-down therapy due to an AE, however, the participant did not require subsequent antibiotic therapy and hence their status for study medication in trial was reported as completed.

Most Frequently Reported Adverse Events

The most frequently reported AEs (incidence ≥5% in either treatment group) were: vomiting (15.3%), diarrhoea (9.4%), nausea (7.1%), abdominal pain (5.9%), headache (5.9%), pyrexia (5.9%), and thrombocytosis (5.9%) in the IMI/REL group, and vomiting (10.7%), diarrhoea (7.1%), nasopharyngitis (7.1%), nausea (7.1%), pyrexia (7.1%), and tachycardia (7.1%) in the Active Control group. The percentage of participants with AEs (incidence ≥12 participants in the IMI/REL group, or ≥2 participants in the Active Control group) was comparable for both intervention groups, except tachycardia, which was reported for 2 participants in the Active Control group and none in the IMI/REL group.

AEs Related to Study Intervention

Overall, the percentage of participants with drug-related AEs (22 [19.5%] participants) was generally comparable for both intervention groups (IMI/REL: 20.0%; Active Control: 17.9%). The most frequently reported drug-related AEs (incidence ≥2 participants in either intervention group) were nausea (3 [3.5%]), vomiting (3 [3.5%]), chromaturia (2 [2.4%]), and pruritus (2 [2.4%]) in the IMI/REL group; and diarrhoea (2 [7.1%]), and nausea (2 [7.1%]) in the Active Control group.

The percentage of participants who had AEs considered by the investigator to be drug related (incidence ≥12 participants in the IMI/REL group or ≥2 participants in the Active Control group) was comparable for both intervention groups.

Serious Adverse Events and Other Clinically Meaningful Adverse Events

There were no AEs reported with an outcome of death in this study.

The percentage of participants with SAEs was comparable for both intervention groups (IMI/REL: 11.8%; Active Control: 10.7%). Most of the SAEs were reported in 1 participant in either treatment group (IMI/REL: calculus urinary, drug intolerance, Escherichia urinary tract infection, food poisoning, and short-bowel syndrome; Active Control: gastroenteritis rotavirus, neonatal infection, and postoperative wound infection), except for intestinal obstruction reported in 2 (2.4%) participants in the IMI/REL group and urinary tract infection reported in 3 (3.5%) participants in the IMI/REL group. All SAEs were resolved.

No participants had SAEs leading to discontinuation of IV study intervention. Two participants in each intervention group (IMI/REL: 2.4%; Active Control: 7.1%) had SAEs leading to discontinuation of study intervention during oral step-down therapy.

Drug-related Serious Adverse Events

Two (2.4%) participants in the IMI/REL group (calculus urinary and drug intolerance) and none in the Active Control group had SAEs that were considered by the investigator to be drug related. Of these, the SAE of calculus urinary was considered by the investigator to be IV drug related. Study intervention continued with no modification and the SAE was resolved after a duration of 5 days. The SAE of drug intolerance was considered by the investigator to be related to oral step-down therapy. Oral step-down therapy was discontinued and IV therapy resumed. Drug intolerance was resolved 23 hours after its onset and the participant completed the study.

Discontinuations and Interruptions Due to Adverse Events

AEs leading to discontinuation of study intervention were reported for 5 (5.9%) participants in the IMI/REL group and 2 (7.1%) participants in the Active Control group. All of these AEs resolved during the study. AEs leading to discontinuation of IV study intervention were reported in 3 (3.5%) participants in the IMI/REL group (peripheral swelling, rash, and rash erythematous) and none in the Active Control group. Of these, the AEs of rash and rash erythematous were considered by the investigator to be IV drug related.

Adverse Events of Special Interest

No cases of elevated liver enzymes or potential drug-induced liver injury events meeting predefined criteria were reported in the study.

Clinical Laboratory Evaluation

Laboratory Values Over Time

The percentage of participants with post-baseline grade increases in laboratory abnormalities during treatment and through the 14-day follow-up period was generally comparable for both intervention groups.

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

No ne of the reported abnormalities in vital signs and physical examination findings were SAEs or AEs leading to discontinuation.

PK results

A table was included with Listing of Individual Plasma Concentrations of IMI/REL Following IV Administration of Concentration-Time Data Imipenem/Cilastatin/Relebactam (IMI/REL) to Participants in Cohorts 1-5. The table is over 100 pages and is not shown here. No summary table was found/ provided.

These data, along with existing paediatric PK data from P020, were used to update the population PK model and calculate the secondary PK endpoints (for REL, plasma exposure [AUC0-24hr], fAUC0-24hr/MIC, and Ceoi; for imipenem, % fT>MIC, plasma exposure [AUC0- 24hr], and Ceoi), which will be presented in a separate paediatric population PK modelling and simulation report.

2.3.3. Discussion on clinical aspects

The submitted study was a Phase 2/3 randomized, active-controlled, parallel-group, multi-site, open-label study of IMI/REL in paediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative bacterial infections. Participants with HAP/VAP, cIAI, or cUTI were randomized in a 3:1 ratio to receive IMI/REL or active control. The study randomised a total of 115 participants.

Efficacy

Efficacy objectives and endpoints were secondary and descriptive in nature. Treatment with IMI/REL resulted in a numerically comparable effect with the comparative treatment regimens of the respective indications HAP/VAP, cIAI and cUTI and studied cohorts. No concerns related to efficacy are noted.

Safety

The safety of IMI/REL was generally comparable to comparator regimens. Reported adverse events were in line with the known safety profile when IMI/REL is used in adults. No new safety concerns were noted.

Pharmacokinetics

The individual plasma concentrations were provided in a very large table, however no summary table was provided. While a summary table (from either NCA or popPK) would have been appreciated. The applicant has stated that the popPK analysis calculating the relevant PK metrics, will be provided in a future type II variation planned for 2025. This is accepted and this issue is therefore not pursued.

3. Overall conclusion and recommendation

The MAH submitted the results of a completed paediatric study included in the paediatric investigational plan. No claims or proposals for updating the product information are made in this submission. No major concerns with regards to efficacy and safety were noted. The benefit-risk balance for the approved indications remains favourable.

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