EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 October 2020
EMA/CHMP/538608/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Recarbrio

International non-proprietary name: imipenem / cilastatin / relebactam

Procedure No. EMEA/H/C/004808/II/0001

Marketing authorisation holder (MAH) Merck Sharp & Dohme B.V.

Note

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

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List of abbreviations

Abbreviation	Definition
FDA	US Food and Drug Administration
FDC	fixed-dose combination
HA(B)P	hospital-acquired (bacterial) pneumonia
ICU	intensive care unit
IMI	imipenem/cilastatin
IMI/REL	imipenem/cilastatin/relebactam
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LFT	liver function test
LRT	lower respiratory tract
MBD	microbroth dilution
MBL	metallo-β -lactamase
MDR	multi-drug resistant
ME	microbiologically-evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	modified intention-to-treat
MK-7655	relebactam
MK-7655A	imipenem/cilastatin/relebactam
mMITT	microbiological modified intention-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
NDA	New Drug Application
PD	pharmacodynamic
PIP/TAZ	piperacillin/tazobactam
PK	pharmacokinetics
PKPD	pharmacokinetic/pharmacodynamic
popPK	population pharmacokinetics
PPV	positive pressure ventilation
PTA	probability of target attainment
QIDP	Qualified Infectious Disease Product
QTc	corrected QT interval
q6h	every 6 hours
REL	relebactam

Abbreviation	Definition
RTI	respiratory tract infection
SAE	serious adverse event
SAM	Summary of Additional Microbiology
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
sSAP	supplemental Statistical Analysis Plan
UK	United Kingdom
ULN	upper limit of normal
US	United States
VA(B)P	ventilator-associated (bacterial) pneumonia
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 9 March 2020 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP), with or without concurrent bacteraemia in adults for Recarbrio; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.
Furthermore, the Marketing authorisation holder (MAH) made editorial corrections and brought the PI in line with the latest QRD template version 10.1.

Version 1.1 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0173/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0173/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH received CHMP advice in 2015 (Procedure No.: EMEA/H/SA/2974/1/2014/III). The MAH has followed the advice given with regards the HAP/VAP study, Protocol 014 (in the advice letter named Protocol 011).

It should be noted that since the time for the SA, indications for betalactam-betalactamase inhibitor (BL-BLI) combinations have been granted when the indication already was approved for the BL alone on the basis of PK/PD considerations to support the BLI dose regimen without the need for a clinical trial in the specific condition.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur : n/a

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	25 Apr 2020	25 Apr 2020
☐	CHMP Co-Rapporteur Assessment Report	19 Jun 2020	n/a
☐	CHMP Rapporteur Assessment Report	19 Jun 2020	17 Jun 2020
☐	PRAC Rapporteur Assessment Report	26 Jun 2020	25 Jun 2020
☐	PRAC members comments	01 Jul 2020	01 Jul 2020
☐	Updated PRAC Rapporteur Assessment Report	02 Jul 2020	n/a
☐	PRAC endorsed relevant sections of the assessment report[3]	09 Jul 2020	09 Jul 2020
☐	CHMP members comments	13 Jul 2020	13 Jul 2020
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 Jul 2020	16 Jul 2020
	CHMP Similarity Report		23 Jul 2020
☐	Request for Supplementary Information	23 Jul 2020	23 Jul 2020
☐	Submission of Responses	14 Aug 2020	11 Aug 2020
☐	Re-start of procedure	17 Aug 2020	17 Aug 2020
☐	CHMP Rapporteur Assessment Report	15 Sep 2020	10 Sep 2020
☐	PRAC Rapporteur Assessment Report	18 Sep 2020	17 Sep 2020
☐	PRAC members comments	23 Sep 2020	23 Sep 2020
☐	Updated PRAC Rapporteur Assessment Report	24 Sep 2020	n/a
☐	PRAC endorsed relevant sections of the assessment report[3]	01 Oct 2020	01 Oct 2020
☐	CHMP members comments	05 Oct 2020	05 Oct 2020
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	08 Oct 2020	08 Oct 2020
☒	Opinion	15 Oct 2020	15 Oct 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

In addition to the already authorised indication for use, the MAH proposes Recarbrio to be indicated for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in adults and for the treatment of bacteraemia that occurs in association with, or is suspected to be associated with HAP/VAP.

Epidemiology

HAP and VAP are among the most common hospital-acquired infections. Globally, pneumonia is one of the most common nosocomial infections with reported incidence estimates of up to 1.6% of hospital admissions. Mortality in patients with HAP/VAP are at least 20%.

Aetiology and pathogenesis

HAP and VAP are serious hospital-acquired lung infections occurring after more than 48 hours of hospitalisation or within 7 days after discharge from a hospital (for HAP) or at least 48 hours after mechanical ventilation (for VAP). HAP/VAP can occur with or without concurrent bacteraemia.

Among commonly isolated pathogens in HAP/VAP are *Staphylococcus aureus* (methicillin susceptible or resistant), Enterobacterales and non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* spp.

Clinical presentation, diagnosis

HAP and VAP are diagnosed based on clinical presentations and radiologic imaging in addition to microbiological investigations to characterise the pathogens causing the infection.

Management

Treatment of HAP and VAP is empiric. According to international guidelines, initial antibacterial regimens should be designed to be active against the most commonly isolated pathogens and take into account mortality risk factors and likelihood of infections caused by methicillin-resistant *S. aureus* and MDR Gram-negative pathogens.

Beta-lactam antibacterial agents are commonly used. Increasing resistance to beta-lactams, including the carbapenems, has led to some organisms being effectively untreatable or treatable only by a few alternative agents. The European Centre for Disease Prevention and Control (ECDC) estimate that nearly 700,000 infections and 33,000 deaths in the EU and European Economic Area (EEA) in 2015 are a consequence of MDR bacterial infection (Cassini et al. 2019). The burden has increased since 2007. Carbapenem-resistance (CR) in *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* contributed significantly to the number of estimated deaths (approximately 4,000 and 2,000 deaths, respectively) whereas the numbers of deaths

estimated to be caused by infections caused by CR *Escherichia coli* was lower (~100). In 2013 to 2014, the *Klebsiella pneumoniae* carbapenemase (KPC) and oxacillinase-48 (OXA-48) was the most widely disseminated carbapenemases across Europe (Grundmann et al. 2017). Metallo-beta-lactamases such as New-Delhi metallo-betalactamase (NDM) and Verona integron-encoded metallo-β-lactamase (VIM) were detected to a lesser extent. There remains an unmet medical need for additional antibacterial agents addressing carbapenem resistance in Gram-negative organisms.

2.1.2. About the product

Imipenem is a carbapenem β-lactam antibacterial agent that inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins (PBPs). PBPs are enzymes involved in the last steps of peptidoglycan synthesis. Imipenem is not hydrolysed by, and thus stable to the majority of serine β-lactamases. Cilastatin (CIL) is a renal dehydropeptidase inhibitor that limits the renal metabolism of IMI. CIL does not have antibacterial activity. Relebactam (REL) is a diazabicyclooctane (DABCO) β-lactamase inhibitor that inhibits a variety of Ambler class A and C but not class B and D β-lactamases. REL has in itself no significant antibacterial activity at clinically relevant doses. The role of REL in the FDC is to restore the activity of imipenem in imipenem-resistant gram-negative infections when the resistance is caused by production of β-lactamases within the spectrum of REL´s inhibitory activity.

Recarbrio is authorised within the EU for the treatment of infections due to aerobe Gram-negative microorganisms in adults with limited treatment options.

Recarbrio is for intravenous use.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

The submitted microbiology studies are assessed in the clinical section.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has submitted a rationale for not submitting an environmental risk assessment.

The environmental risk assessment for relebactam was recently approved as part of the MAA of Recarbrio. In the initial ERA for relebactam a conservative approach assuming the maximum dose of 1000 mg/day and a market penetration of 1% with no adjustments for treatment schedules.

The environmental risk assessment for imipenem and cilastatin are on-going and will be submitted in 4Q 2020.

The CHMP noted that in the ERA for relebactam in the MAA, $PEC_{SURFACEWATER}$ was calculated using default values. Relebactam is not classified as a PBT or vPvB candidate. Based on the Phase I PECSW, the risk quotients/ratios were below 0.1 for sludge microorganisms and below 1 for other compartments. From the initial approval of Recarbrio, in terms of the water/sediment study (OECD 308) the DT50 in the water phase at +12 °C for the Weweantic river was 81 days, which exceeds the trigger for very persistent in fresh water (60 days). It was concluded that relebactam was not expected to pose a risk on the environment.

Based on the low risk quotients in the initial ERA (PEC/PNEC surface water 0.08; groundwater 0.005; sediment 0.06; and wastewater treatment facility 0.0005), it seems unlikely that the extension of the indication to include the treatment of hospital-acquired pneumonia including ventilator-associated pneumonia would change the conclusions of the initial ERA.

The CHMP reiterated that the Environmental risk assessment of imipenem and cilastatin needs to be submitted no later than the end of Q4 2020.

2.2.2. Conclusion on the non-clinical aspects

From a non-clinical point of view, the application is approvable.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of relebactam.

Considering the above data, relebactam is not expected to pose a risk to the environment.

The Environmental risk assessment of imipenem and cilastatin needs to be submitted no later than the end of Q4 2020.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
7655A-014 [Ref. 5.3.5.1: P014 MK7655A]	3	Americas Asia Europe Russian Federation	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Piperacillin/Tazobactam in Subjects with Hospital-Acquired Bacterial Pneumonia or Ventilator-Associated Bacterial Pneumonia	Multicenter, double-blind, active-controlled, efficacy, safety, parallel assignment, intervention	IMI/REL: IMI/REL 500 mg/ 250 mg every 6 hours IV infusion PIP/TAZ: PIP/TAZ 4000 mg/ 500 mg every 6 hours IV infusion	Males or females 18 years or older who required IV antibiotic therapy for HABP or VABP	IMI/REL 500 mg/ 250 mg: 266 PIP/TAZ 4000 mg/ 500 mg: 269

2.3.2. Pharmacokinetics

IMI/REL is approved as a powder for solution for infusion provided in a vial for constitution and direct IV infusion. No new formulation was developed for the HAP/VAP clinical program and the same dosage and formulation approved for the initial indication(s) is proposed to treat HAP/VAP infections.

The pharmacokinetics of imipenem, cilastatin, and relebactam in healthy adults and patients with active bacterial infection has previously been studied. Relebactam, as well as cilastatin is primarily excreted unchanged in urine and minimal clinically relevant metabolism occurs. Imipenem is subject to extensive post-excretory metabolism in the kidney by dehydropeptidases, which can be inhibited by cilastatin. Pharmacokinetic parameters were similar for single- and multiple-dose administration due to minimal accumulation. The penetration into pulmonary epithelial lining fluid (ELF) expressed as the total ELF-to-unbound plasma exposure ratio was 55 % and 54 % for imipenem and relebactam, respectively.

A Phase 3 trial in HAP/VAP (P014) has now been conducted. PK samples with a sparse sampling scheme were collected in this trial, and these PK data were integrated with previously submitted Phase 1, Phase 2 and Phase 3 trials data to inform the popPK model and used to generate and describe the PK profile in the target patient population, see below.

2.3.3. Pharmacodynamics

2.3.4. PK/PD modelling

Population pharmacokinetic (popPK) analysis

Population PK models of imipenem and relebactam have previously been developed based on Phase 1, Phase 2 and Phase 3 data. The majority of the patient population in the previously developed model were receiving relebactam and imipenem for complicated urinary tract infections or intra-abdominal infections (cUTI/cIAI).

The primary objectives of the population PK analysis are to:

1. Update the population PK models for imipenem and relebactam using data from studies PN014 and PN017 (see below)
2. Evaluate the effect of pneumonia (including the impact of ventilation) on imipenem and relebactam plasma PK
3. Determine the probability of target attainment (PTA) using simulations to support dose regimen justification

Protocol Number	Design / Objective	Number of Subjects / Patient Population	Imipenem Doses	Relebactam Doses
PN014	Randomized (1:1), double-blind, active-controlled study to evaluate the efficacy (incidence rate of all-cause mortality) of relebactam/imipenem versus pipericillin/tazobactam in subjects with HABP/VABP	Approximately 236 (half of 536) hospitalized adults (≥ 18 years) with HABP/ VABP	500/250mg imipenem + relebactam (as FDC) q6h MD administered for 7 to 14 days	
PN017	This is a nonrandomized, non-controlled, multi-site, open-label trial the to evaluate the safety and efficacy of imipenem/cilastatin/relebactam in Japanese subjects with cIAI or cUTI	83 Japanese subjects with cIAI or cUTI	500/250mg imipenem + relebactam (as FDC) q6h MD administered for 5 to 14 days	

For normal subjects with creatinine clearance (CrCL) >90 mL/min, dose of IMI/REL is imipenem 500mg, cilastatin 500 mg and relebactam 250mg. Patients who have a CrCL less than 90mL/min require dosage reduction of IMI/REL, see table below.

Table popPK1. Dosage of IMI/REL in Adults with renal impairment

Estimated CrCL(mL/min)[a]	Recommended Dosage of IMI/REL (imipenem/cilastatin and relebactam) (mg)[b]	Dosing Interval
60 to 89	1 gram (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)	Every 6 hours
30 to 59	0.75 grams (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)	Every 6 hours
15 to 29	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours
End Stage Renal Disease (ESRD) on Hemodialysis[c]	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours

[a]CrCL calculated using the Cockroft-Gault formula
[b]Administer by IV over 30 minutes.
[c]Administration should be timed to follow hemodialysis.
IMI/REL is provided as a single vial in a fixed-dose combination; the dose for each component will be adjusted equally during preparation

Methods

The population PK analysis was performed using a non-linear mixed effects modelling approach. Model selection was based on the Log-Likelihood criterion, goodness of fit plots, and scientific plausibility. The prior model was updated with the new data and a limited covariate search was conducted to update the model; identification of covariates was performed using automated stepwise covariate model building (SCM). The following covariates were investigated in the SCM process: race, infection type (cUTI, cIAI, pneumonia) and ventilation status. Creatinine clearance (CrCL) and weight (WT) effects were included in the model a-priori.

Final models

The existing population PK model was updated with study data from PN014 and PN017. The resulting model structure was able to capture the new PK data whilst maintaining goodness of fit for the existing data. The PK of both compounds was characterized by a two-compartment model with IV infusion, central volume of distribution (V1), peripheral volume of distribution (V2), inter-compartmental clearance (Q) and linear clearance (CL) from the central compartment. Between subject variability terms were included on CL, V1 and V2 and a proportional model was used for the residual error. Correlations between CL and V1 were captured with a covariance term for both compounds. Creatinine clearance (CrCL) and weight (WT) effects were included in the model a-priori. See table below for final models. pvVPC are depicted in figure below.

Table popPK2. IMI and REL Final model parameter estimates

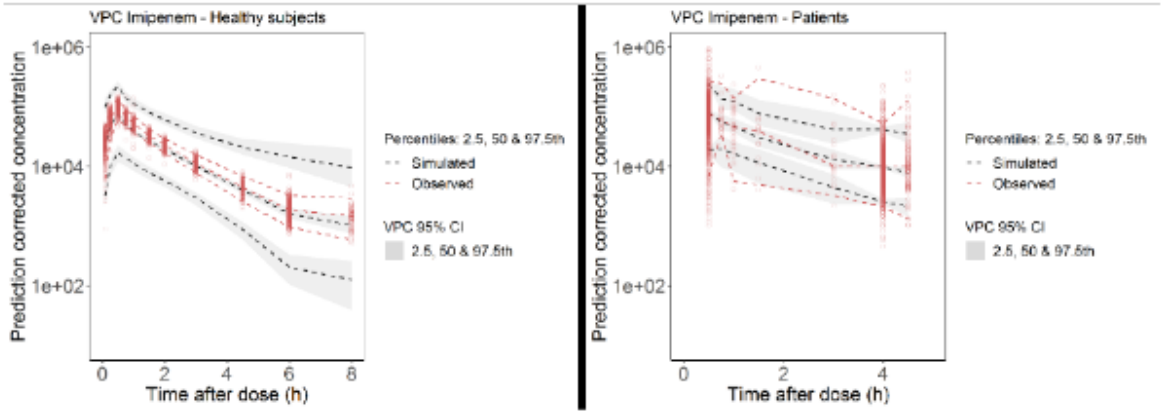
	Imipenem				Relebactam			
	NONMEM		Bootstrap[d]		NONMEM		Bootstrap	
Parameter	[a]Estimate [b](RSE%)	[c]95% CI	Estimate (RSE%)	95% CI	Estimate (RSE%)	95% CI	Estimate (RSE%)	95% CI
CL (L/h)	12.68 (1.7)	12.25 - 13.11	12.69 (1.7)	12.25 - 13.13	7.23 (1.6)	7 - 7.47	7.23 (1.5)	7.03 - 7.45
V1 (L)	11.39 (3.8)	10.52 - 12.27	11.45 (5.4)	10.34 - 12.72	11.21 (2.7)	10.61 - 11.81	11.22 (2.8)	10.56 - 11.86
V2 (L)	7.79 (5.7)	6.9 - 8.68	7.76 (7.3)	6.58 - 8.74	6.15 (3.8)	5.68 - 6.62	6.16 (4.1)	5.66 - 6.69
Q (L/h)	23.06 (10.9)	18.02 - 28.1	22.91(15.2)	16.23 - 29.75	10.93 (7.8)	9.22 - 12.63	10.89 (9.5)	8.82 - 13.07
Covariates on CL								
CrCL (power)	0.48 (4.0)	0.44 - 0.52	0.48 (4.3)	0.44 - 0.52	0.75 (4.2)	0.68 - 0.81	0.75 (4.5)	0.68 - 0.81
WT (power)	0.29 (17.7)	0.19 - 0.39	0.29 (26.1)	0.13 - 0.43	na	na	Na	na
[g]Pneunomia	-0.38 (7.7)	-0.44 - -0.32	-0.38 (7.5)	-0.44 - -0.32	-0.43 (5.0)	-0.48 - -0.39	-0.43 (5.0)	-0.47 - -0.39
Covariates on V1								
WT (power)	1.03 (9.7)	0.83 - 1.23	1.03 (14.5)	0.75 - 1.31	0.65 (10.7)	0.51 - 0.79	0.66 (12.8)	0.49 - 0.83
[g]Pneumonia	-0.39 (15.5)	-0.52 - -0.27	-0.39 (16.4)	-0.50 - -0.25	-0.29 (16.2)	-0.38 - -0.19	-0.28 (17.8)	-0.38 - -0.18
[h]Ventilation	0.23 (46.2)	0.02 - 0.45	0.24 (47.2)	0.02 - 0.48	0.36 (32.0)	0.13 - 0.58	0.36 (31.8)	0.15 - 0.58
Random effects BSV	[e]CV% [b](RSE%)		CV% (RSE%)		CV% (RSE%) shrink		CV% (RSE%)	
BSV in CL	53.0 (9.4) 7.2	47.8 - 57.8	53.0 (9.2)	48.0 - 57.4	43.6 (8.1) 13.9	39.9 - 47	43.4 (8.1)	40.0 - 46.9
BSV in V1	86.3 (14.0) 8.7	73.2 - 97.6	86.8 (13.6)	75.5 – 99.0	56.1 (10.1) 18.8	50.1 - 61.6	55.7 (10.7)	50.0 - 61.6
BSV in V2	63.5 (14.7) 35.6	53.3 - 72.2	63.1 (19.4)	52.9 - 77.5	58.7 (26.2) 49.5	40.5 - 72.5	58.4 (29.8)	40.0 - 76.8
[f]Corr CL ~ V1	0.97	-	0.97	-	0.62	-	0.62	-
Random effects BSV	CV% (RSE%) shrink		CV% (RSE%)		CV% (RSE%) shrink		CV% (RSE%)	
Residual Error, prop	29.5 (7.4) 14.1	27.2 - 31.6	29.4 (7.3)	26.5 - 31.6	22.6 (6.7) 14.0	21 - 24	22.5 (6.5)	20.0 - 24.5

	Imipenem				Relebactam			
	NONMEM		Bootstrap[d]		NONMEM		Bootstrap	
Parameter	[a]Estimate [b](RSE%)	[c]95% CI	Estimate (RSE%)	95% CI	Estimate (RSE%)	95% CI	Estimate (RSE%)	95% CI

[a] Mean parameter estimate
[b] % RSE derived from the following equation: (standard error / mean) x 100
[c] 2.5th and 97.5th percentile confidence intervals
[d] Bootstrap is based on n=1000 dataset replicates
[e] Obtained according to the following equation: * %CV = $\sqrt{\omega^2} * 100$
[f] Corr: correlation between variance parameters calculated as $\omega_{ij}^2/\text{sqrt}(\omega_{ii}^2*\omega_{jj}^2)$
[g] Reference group is healthy/cIAI/cUTI subjects combined
[h] The ventilation effect on Pneumonia subject receiving ventilation. Reference group is pneumonia subjects
Abbreviations: BSV: Between Subject Variability; CI: Confidence Interval; Corr: Correlation coefficient; CV: Coefficient of Variance; RSE: Relative Standard Error; shrink: Shrinkage; na, not applicable; prop, proportional
Source: Merck-7655A/Analysis/e-model-finalization/run105.lst
Merck-7655A/Analysis/r-scripts/nonmem-output-v2.R
Merck-7655A/Analysis/r-scripts/bootstrap-plots-v2.R

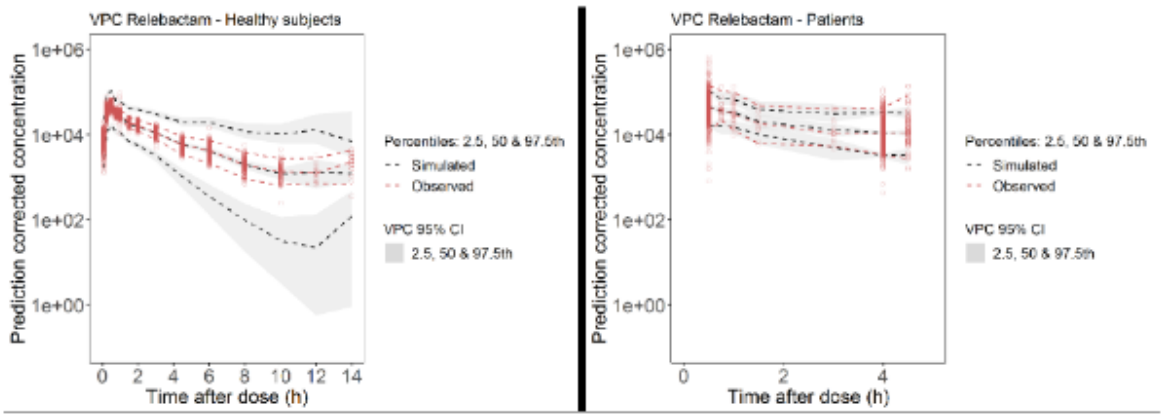
Figure popPK1. pcVPCs for IMI (top) and REL (bottom)

Figure 19 pcVPC Stratified by Health Status for Imipenem (Semi-Logarithmic Scale)



Source: Merck-7655A/Analysis/r-scripts/vpc-healthy-imi.R
Merck-7655A/Analysis/r-scripts/vpc-patient-imi.R
Notes: Dashed lines represent 2.5th, median and 97.5th percentile concentrations values. Red = observed concentrations; Black = model predicted concentrations. Shaded areas represent the 95th confidence interval (CI) around the 5th, median and 95th model predictions.
Healthy = healthy volunteers without infection.; Patient = all patients with infection (cIAI, Cuti, Pneumonia)

Figure 20 pcVPC Stratified by Health Status for Relebactam (Semi-Logarithmic Scale)

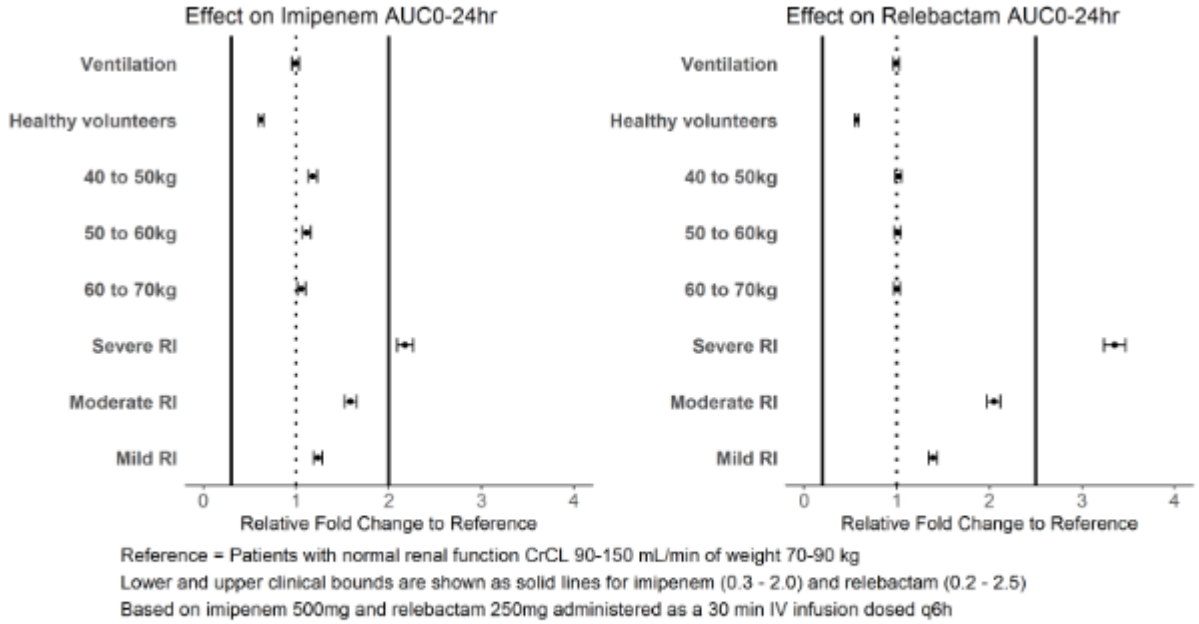


Source: Merck-7655A/Analysis/r-scripts/vpc-healthy-rel.R
Merck-7655A/Analysis/r-scripts/vpc-patient-rel.R
Notes: Dashed lines represent 2.5th, median and 97.5th percentile concentrations values. Red = observed concentrations; Black = model predicted concentrations. Shaded areas represent the 95th confidence interval (CI) around the 5th, median and 95th model predictions.
Healthy = healthy volunteers without infection.; Patient = all patients with infection (cIAI, cUTI, HABP/VABP)

Exposure in target population

Impact of intrinsic factors are shown in figure below.

Figure popPK2. Impact of Intrinsic Factors on Simulated steady state AUC 0-4 h of IMI/REL



Source: Merck-7655A/Analysis/k-simulations/simulation-forest-plot-auc-v2.R

PopPK conclusion

The existing population PK model was successfully updated to include data from PN014 and PN017. The model was able to adequately characterize the new PK data. Pneumonia and ventilation status were identified as statistically significant covariates affecting the PK of imipenem and relebactam.

Probability of target attainment (PTA)

Methods for PTA simulation

Demographic data for PTA simulations was pooled from subjects with HAP/VAP in PN014 (MK-7655) and ESRD subjects in MK-3415 to create two data pools, one for non-ventilated pneumonia (n=178) and the other for ventilated pneumonia (n=161), see tables below. The simulations performed included both unexplained between subject and residual error variability, from the final PK model.

Table popPK3. Demographics of the Virtual Non-ventilated Subjects Generated for the Simulations

	Minimum	Q1	Median	Q3	Max
End Stage Renal Disease (CrCL = <15 mL/min) n=500					
CrCL (mL/min)	4.7	8.4	10.7	13.0	15.0
Weight (kg)	26.0	45.9	55.0	65.5	116.7
Severe Renal Impairment (CrCL = 15 – 30 mL/min) n=500					
CrCL (mL/min)	15.0	18.6	22.6	26.0	30.0
Weight (kg)	28.7	51.0	61.6	72.7	124.1
Moderate Renal Impairment (CrCL = 30 – 60 mL/min) n=500					
CrCL (mL/min)	30.0	35.2	42.1	49.4	59.9
Weight (kg)	30.7	56.0	67.5	78.9	125.3
Mild Renal Impairment (CrCL = 60 – 90 mL/min) n=500					
CrCL (mL/min)	60.0	65.9	72.1	80.3	89.8
Weight (kg)	32.6	59.4	70.9	84.2	136.9
Normal Renal Function (CrCL = 90 – 150 mL/min) n=500					
CrCL (mL/min)	90.1	102.4	112.6	128.1	150.0
Weight (kg)	27.7	62.5	73.0	87.3	191.6
Augmented Renal Function (CrCL = 150 - 180 mL/min) n=500					
CrCL (mL/min)	150.0	156.8	164.3	171.0	179.9
Weight (kg)	39.2	64.7	76.8	92.4	147.4
Augmented Renal Function (CrCL = 180 - 210 mL/min) n=500					
CrCL (mL/min)	180.0	186.5	193.7	200.0	209.6
Weight (kg)	34.8	68.7	80.1	93.0	166.7
Augmented Renal Function (CrCL = 210 - 250 mL/min) n=500					
CrCL (mL/min)	210.0	218.7	227.5	238.2	250.0
Weight (kg)	39.1	67.7	82.0	96.8	185.2

Source: Merck-7655A/Analysis/r-scripts/creating-simulation-datasets-ss-nonvent.R

Table popPK4. Demographics of the Virtual ventilated Subjects Generated for the Simulations

	Minimum	Q1	Median	Q3	Max
End Stage Renal Disease (CrCL = <15 mL/min) n=500					
CrCL (mL/min)	4.1	7.9	10.4	12.7	15.0
Weight (kg)	34.0	52.5	61.6	72.3	125.3
Severe Renal Impairment (CrCL = 15 – 30 mL/min) n=500					
CrCL (mL/min)	15.0	18.7	22.0	25.8	30.0
Weight (kg)	38.7	56.3	65.8	76.1	130.9
Moderate Renal Impairment (CrCL = 30 – 60 mL/min) n=500					
CrCL (mL/min)	30.0	36.8	43.5	51.2	59.9
Weight (kg)	34.8	61.6	71.9	82.5	134.8
Mild Renal Impairment (CrCL = 60 – 90 mL/min) n=500					
CrCL (mL/min)	60.1	66.4	73.0	80.4	89.9
Weight (kg)	38.2	64.4	74.7	86.4	152.8
Normal Renal Function (CrCL = 90 – 150 mL/min) n=500					
CrCL (mL/min)	90.0	101.7	114.5	129.8	149.7
Weight (kg)	37.8	68.0	77.7	89.4	136.8
Augmented Renal Function (CrCL = 150 - 180 mL/min) n=500					
CrCL (mL/min)	150.0	157.0	164.3	172.3	180.0
Weight (kg)	45.7	69.0	80.0	93.2	160.8
Augmented Renal Function (CrCL = 180 - 210 mL/min) n=500					
CrCL (mL/min)	180.2	186.5	193.8	201.4	209.9
Weight (kg)	39.9	72.2	82.0	95.4	168.3
Augmented Renal Function (CrCL = 210 - 250 mL/min) n=500					
CrCL (mL/min)	210.1	218.7	227.7	237.8	249.7
Weight (kg)	43.3	72.0	85.2	96.8	155.9

Source: Merck-7655A/Analysis/r-scripts/creating-simulation-datasets-ss-vent.R

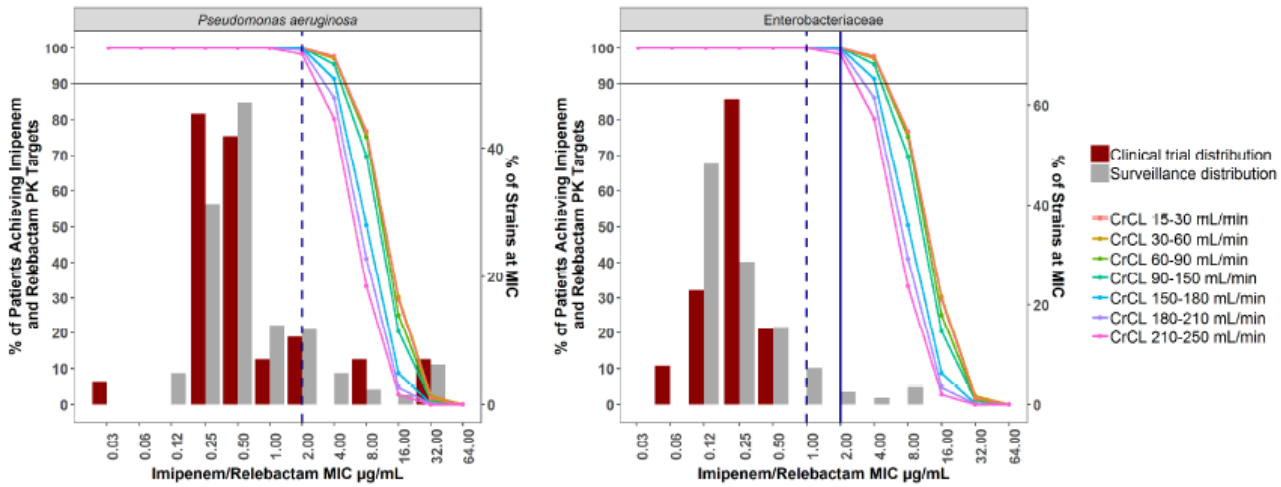
Summary of support for dose selection

Monte Carlo simulation analyses employed the final popPK models of both REL and IMI, and aimed to confirm the appropriateness of the dosing regimens studied in the HAP/VAP trial and to support the proposed susceptibility testing interpretive criteria assessing the joint probability of target attainment (PTA) of both imipenem and REL PK/PD targets (PDTs). The PDTs used in this PTA assessment were 30% *f*T>MIC for imipenem (correlating with 90% animal survival in in vivo animal models) and *f*AUC0-24hr/MIC≥8 for REL (corresponding to 2-$\log_{10}$ kill in murine thigh and lung infection models). A sensitivity analysis of joint PTA with an imipenem PDT of 40% *f*T>MIC (corresponding to 2-$\log_{10}$ kill in animal models of infection) and REL PDT of *f*AUC0-24hr/MIC≥8 was also performed. PTA for the more conservative sensitivity analysis is shown in the table and figures below.

Table PD1. Percentage of HAP/VAP patients achieving 40% of *f*T>MIC for imipenem and *f*AUC/MIC=8.0 for REL at steady state

CrCL	Percentage of Patients Achieving 40% of *f*T>MIC for Imipenem and *f*AUC/MIC=8 for Relebactam											
MIC (µg/mL)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
<15 mL/min	100	100	100	100	100	100	100	99.9	93.2	58.0	15.4	0.6
15 - 30 mL/min	100	100	100	100	100	100	100	97.7	76.8	29.4	1.8	0
30 - 60 mL/min	100	100	100	100	100	100	100	97.0	76.6	30.2	2.4	0.1
60 - 90 mL/min	100	100	100	100	100	100	100	97.2	75.2	25.1	1.4	0
90 - 150 mL/min	100	100	100	100	100	100	100	95.4	69.9	20.4	1.2	0
150 - 180 mL/min	100	100	100	100	100	100	99.9	91.3	50.4	8.7	0.3	0
180 - 210 mL/min	100	100	100	100	100	100	99.4	86.1	41.1	4.7	0.2	0
210 - 250 mL/min	100	100	100	100	100	99.9	98.2	80.2	33.2	2.8	0	0

Figure PD1. Percentage of patients achieving 40% *f*T>MIC for imipenem and *f*AUC/MIC=8.0 for REL with *P. aeruginosa* (left) and Enterobacteriaceae (right) MIC distributions amongst isolates relevant to proposed indication from clinical P014 and surveillance data



2.3.5. Discussion on clinical pharmacology

PopPK analysis

Updating the existing popPK dataset with data from studies PN014 and PN017 and starting from the prior models is supported. Including creatinine clearance (CrCL) and weight (WT) effects in the models a-priori is supported. The pcVPCs for healthy subject show that the updated models can describe the median tendencies however variability is overpredicted for both imipenem and relebactam. The imipenem VPC for patients look better but underpredicts upper percentiles. This means that the model simulates slightly lower exposure for some patients than what is observed, and this can be considered conservative and acceptable for PTA. The relebactam pcVPC in patients looks adequate. PTA are not simulated in healthy subjects, thus the overpredicted variability in healthy subjects is not deemed an issue.

In the MMA the MAH has updated the popPK models for both imipenem and relebactam with bodyweight based allometric scaling with fixed exponents and provided updated VPCs. The parameter estimates were similar to the final models, and the RSEs were reasonable, both for imipenem and for relebactam. Thus,

shortcomings of the models were previously assessed, and the updated models here are also generally deemed adequate for PTA simulations.

The MAH appears to pool HAP patients with other patients such as cUTI and cIAI patients as pneumonia is not shown in figure popPK2. The model identified a lower clearance in pneumonia patients for both imipenem and relebactam. The difference in PK between pneumonia patients and other patients needs to be further discussed with regards augmented renal clearance. Bacteraemia does not appear to have been tested as a covariate in the models.

The popPK models are generally deemed adequate for PTA simulations. There is however a question regarding patients with augmented renal clearance and the MAH's proposal in the SmPC. Also, bacteraemia should be tested as a covariate for REL, see also *support for dose selection* below.

Support for dose selection

The acceptance of the applied indications for Recarbrio, already approved for IMI alone, is dependent on PK/PD considerations to demonstrate that the dose of REL is sufficient to protect IMI from hydrolysis of relevant beta-lactamases in HAP/VAP with or without associated bacteraemia. It was not expected, nor requested, that the HAP/VAP study should enrol sufficient organisms that were resistant to IMI but susceptible to IMI/REL to demonstrate a clinical benefit of adding REL and/or substantiate the adequacy of the REL dose regimen. Therefore, the PTA analyses to support the dose regimens and data to demonstrate that REL adequately penetrates to the lung, i.e. epithelial lining fluid (ELF), are of paramount importance.

The doses used in the HAP/VAP study (500/500/250 mg q6h adjusted for renal function) are similar to those recommended in the product information for Recarbrio for the treatment of infections due to aerobe Gram-negative microorganisms in adults with limited treatment options.

Based on plasma PTA simulations using relevant PDTs of up to 40% *f*T>MIC PDTs for imipenem corresponding to 2-$\log_{10}$ kill in animal models of infection and *f*AUC0-24hr/MIC≥8 for REL corresponding to 2-$\log_{10}$ kill in murine thigh and lung infection models, the doses of IMI and REL in different renal function categories including augmented renal clearance (ARC) up to a CrCL of 250 mL/min are satisfactory (PTA >90%) for the treatment of HAP/VAP caused by pathogens having MICs up to 2 mg/L.

In the initial registration of Recarbrio the MAH provided data to support that ELF penetration in healthy subjects is 50-60% compared with plasma concentrations for both IMI and REL, a level considered acceptable for IMI alone for the treatment of HAP/VAP without dose adjustments compared with other indications. Although PDTs in ELF are not established for imipenem and REL, PTA data taking the ELF penetration into account was requested to support that the doses proposed for REL are adequate in HAP/VAP. Additional PTA analyses by accounting for ELF penetration using 1 and 2-$\log_{10}$ kill targets derived from the neutropenic murine thigh model (30% and 40% *f*T>MIC for imipenem and *f*AUC/MIC=4.3 and 7.0 adjusted for ELF penetration for REL) are supportive of the adequacy of the doses of IMI and REL for the treatment of HAP/VAP for all renal function categories up to an MIC of 2 mg/L. Treatment of HAP/VAP with associated bacteraemia is already granted for IMI when used alone. Therefore, there is no concern regarding the IMI doses to treat patients who have bacteraemia in association with HAP/VAP. REL concentration-time profiles and clearance were essentially similar for subjects with and without bacteraemia which supports the doses recommended for REL also for subjects with HAP/VAP and associated bacteraemia.

Based on PTA simulations for the HAP/VAP population the MAH proposes to update the SmPC sections 4.2 and 4.4 which formerly conveyed that the dose that is recommended for patients with CrCl ≥ 90 to < 150 mL/min may not be sufficient to treat patients with CrCl ≥ 150 mL/min because in the PTA simulations provided at approval were not satisfactory (PTA <90%) in subjects with augmented renal clearance (ARC). The proposal is to change the cut-off for the HAP/VAP population to ≥250 ml/min which is acceptable. The difference in the PTA simulations seems to be explained by a higher exposure (due to lower clearance) of

imipenem and REL in subjects with HAP/VAP. The previous PTA simulations from the MAA are still considered valid for cIAI and cUTI patients.

2.3.6. Conclusions on clinical pharmacology

The acceptance of the applied indications for Recarbrio is mainly based on PK/PD considerations to demonstrate that the dose of REL is sufficient to protect imipenem from hydrolysis of relevant beta-lactamases in HAP/VAP with or without associated bacteraemia. All issues are resolved.

2.4. Clinical efficacy

2.4.1. Main study

A Phase III, randomized, double-blind, active comparator-controlled clinical trial to study the safety, tolerability, and efficacy of imipenem/cilastatin/relebactam (MK-7655A) versus piperacillin/tazobactam in subjects with hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia (P014)

P014 (also known as MK-7655A-014 or RESTORE-IMI 2) was a phase 3 randomised, double-blind, active comparator trial to evaluate the safety, tolerability, and efficacy of IMI/REL versus PIP/TAZ in hospitalised participants with HAP/VAP.

Methods

Study participants

Key inclusion criteria included the following:

1. ≥ 18 years of age

2. Require treatment with IV antibiotic therapy for HAP or VAP

3. Clinical and radiographic criteria described below, with onset of criteria occurring after more than 48 hours of hospitalization or within 7 days after discharge from a hospital (for HAP) or at least 48 hours after mechanical ventilation (for VAP):

(a) Subject had at least one of the following clinical features:

- New onset or worsening pulmonary symptoms or signs, such as cough, dyspnoea, tachypnoea (e.g., respiratory rate greater than 25 breaths per minute), expectorated sputum production, or requirement for mechanical ventilation
- Hypoxemia (e.g., a partial pressure of oxygen less than 60 millimetres of mercury while the subject is breathing room air, as determined by ABG or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen [PaO2/FiO2])
- Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO2/FiO2) or needed changes in the amount of positive end-expiratory pressure
- New onset of suctioned respiratory secretions

AND

(b) Subject had at least one of the following signs:

- Documented fever (e.g., body temperature ≥38 degrees Celsius)
- Hypothermia (e.g., core body temperature ≤35 degrees Celsius)
- Total peripheral WBC ≥10,000 cells/mm3
- Leukopenia with total WBC ≤4,500 cells/mm3
- Greater than 15 percent immature neutrophils (bands) noted on peripheral
- blood smear

AND

(c) Subject had a chest radiograph showing the presence of a new or progressive infiltrate(s) suggestive of bacterial pneumonia

4. Adequate baseline (at or within 48 hours of screening) lower respiratory tract specimen obtained for Gram stain and culture.

Key exclusion criteria included the following:

1. A baseline LRT specimen Gram stain that shows the presence of Gram-positive cocci only.
2. Confirmed or suspected CAP.
3. Confirmed or suspected pneumonia of viral, fungal, or parasitic aetiology.
4. Active immunosuppression, defined as either receiving immunosuppressive medications or having a medical condition associated with immunodeficiency.
5. Expected to survive <72 hours.
6. Had received effective antibacterial drug therapy for the index infection of HAP/VAP for a continuous duration of more than 24 hours during the previous 72 hours.
7. An estimated or actual creatinine clearance of <15 mL/min at screening, based on the findings of local laboratory values.
8. Undergoing haemodialysis or peritoneal dialysis.

Treatments

Table E1. Study treatments

Drug[a]	Dose/Potency[b]	Dose Frequency	Route of Administration	Regimen/ Treatment Period[c]	Use
Treatment Group 1 (N=268)					
IMI/REL	IMI/REL 500 mg/500 mg/250 mg	Every 6 hours	IV	7 to 14 days	Experimental
Treatment Group 2 (N=268)					
PIP/TAZ	PIP/TAZ 4000 mg/500 mg	Every 6 hours	IV	7 to 14 days	Active Comparator

FDC = fixed-dose combination; IMI = imipenem/cilastatin; IV = intravenous; PIP = Piperacillin; REL = relebactam; TAZ = tazobactam.

[a] IMI/REL and PIP/TAZ were each provided as a FDC in a single vial. IMI/REL also includes 500 mg of cilastatin within the FDC.
[b] Adjustments to dosage of IMI/REL or PIP/TAZ were required for participants with renal insufficiency (Please reference Table 8 and Table 9 in Section 5.2.1.1 of the protocol [16.1.1]).
[c] IV trial treatment was to be administered for a minimum of 168 hours (7 full days). Seven full days of therapy corresponds to 28 doses of IMI/REL (Treatment Group 1) and PIP/TAZ (Treatment Group 2) for every 6 hours. The total duration of IV trial treatment should not have exceeded 14 days.

Participants with concurrent bacteraemia or an infection due to *P. aeruginosa* were to receive 14 days of treatment.

The use of initial empiric treatment with open-label IV linezolid (600 mg every 12 hours) for MRSA infection was required. Linezolid treatment was stopped if the final culture results from the baseline LRT sample did not demonstrate the presence of MRSA.

Objectives

The primary objective (EU SAP) (which was the key secondary objective for the US FDA) was to evaluate the efficacy of IMI/REL versus PIP/TAZ with respect to clinical response at the early follow-up (EFU) visit 7 to 14 days after the end of therapy (EOT) for subjects diagnosed with HAP/VAP in the modified intention-to-treat (MITT) population.

The key secondary objective (primary objective for the US FDA) was to determine the incidence rate of all-cause mortality through Day 28 post-randomisation associated with treatment with IMI/REL compared to treatment with PIP/TAZ in subjects diagnosed with HAP/VAP in the MITT population.

Other secondary objectives were to:

- evaluate the safety and tolerability profile of IMI/REL vs. PIP/TAZ in subjects with HAP/VAP,
- determine the incidence rate of all-cause mortality through Day 28 post-randomization in subjects treated with IMI/REL versus PIP/TAZ based on pneumonia type (non-ventilated HAP, ventilated HAP/VAP) in the MITT population and microbiological modified intention-to-treat (mMITT) population,
- evaluate the efficacy of IMI/REL versus PIP/TAZ with respect to clinical response at the EFU visit for subjects diagnosed with HAP/VAP in the clinically evaluable (CE) population,
- evaluate the efficacy of IMI/REL versus PIP/TAZ with respect to microbiological response at the EOT visit and at the EFU visit for subjects diagnosed with HAP/VAP in the mMITT population and microbiologically evaluable (ME) population.

Outcomes/endpoints

Primary endpoint (EU SAP) (key secondary endpoint US FDA):

- Clinical response at the EFU visit in the MITT population

Key secondary endpoint (primary endpoint US FDA):

- All-cause mortality through Day 28 in the MITT population

Other secondary endpoints:

- Adverse events (AEs) and clinical laboratory assessments
- All-cause mortality through Day 28 in the MITT and mMITT populations
- Clinical response at the EFU visit in the CE population
- Microbiological response at the EOT and EFU visits in the mMITT and ME populations

Sample size

The sample size was primarily based on the US FDA primary endpoint. The planned sample size of 268 subjects per group would provide 84% power to reject the null hypothesis that the true difference in clinical response at the EFU visit exceeds the NI margin of 12.5% assuming true rates for both the control and experimental regimens of 60% (1-tailed alpha of 2.5%).

For the incidence rate of all-cause mortality through Day 28, the NI margin was 10% and the true rate was assumed to be 15% in both treatment arms.

Randomisation

Approximately 536 subjects were to be randomised in a 1:1 ratio. Randomisation was stratified through an interactive voice response system / integrated web response system (IVRS/IWRS) based on 2 factors: ventilation status at randomisation (non-ventilated HAP versus ventilated HAP or VAP) and APACHE II score (<15 versus ≥15). In addition, randomisation was controlled such that approximately 50% of randomised subjects were to be in the VAP or ventilated HAP stratum.

Blinding (masking)

A double-blind/masking technique was used. An unblinded study pharmacist was responsible for preparing the IV study therapy at each study site. Due to a visual difference in the appearance of study treatment solutions, the infusion bags were covered with an opaque sleeve to ensure that other study personnel and all subjects remain blinded to clinical material assignments.

Statistical methods

The primary endpoint was the difference in percentage of subjects achieving a favourable clinical response at EFU. A favourable clinical response at EFU required an assessment of "cure" or "sustained cure". To be considered "sustained cure", the clinical response for the prior visit (EOT) must have been considered "cure". Clinical Response Rating at the EFU Visit, and Day 28 Post-Randomisation Visit, were defined as shown in the table below:

Clinical Response[a]	Response Definition
Sustained Cure	All pre-therapy signs and symptoms[b] of the index infection have resolved (or returned to "pre-infection status") with no evidence of resurgence **AND** no additional antibiotic therapy was required for the index infection.
Cure	All pre-therapy signs and symptoms[b] of the index infection have resolved (or returned to "pre-infection status") **AND** no additional antibiotic therapy is required for the index infection.
Failure	No apparent or insufficient response to IV study therapy in pre-study signs and symptoms of the index infection: persistence, progression, or improvement (without full resolution) of all pre-therapy signs and symptoms[b]
Relapse	Subjects with a favorable clinical response (cure or improved) at the EOT visit have worsening signs and symptoms[b] of the index infection by the EFU or Day 28 post-randomization visit.
Indeterminate	Study data are not available for evaluation of efficacy for any reasons, including: a) Complication related to underlying medical condition; **OR** b) Subject was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical response; **OR** c) Extenuating circumstances (e.g., a major protocol violation) preclude classification as "sustained cure," "failure," or "relapse;" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.

Primary and the key secondary endpoint analysis

For the primary hypothesis (clinical response), IMI/REL was compared to PIP/TAZ using the stratified Miettinen and Nurminen method. IMI/REL was to be considered non-inferior (NI) to PIP/TAZ if the lower bound of the 2-sided 95% confidence interval (CI) for the difference in percentages between the treatment groups (IMI/REL minus PIP/TAZ) is greater than -12.5%. If non-inferiority was established, then superiority of IMI/REL compared to PIP/TAZ was to be evaluated. The same analysis approach was used also for the key

secondary endpoint (all-cause mortality). The analyses were stratified by 1) pneumonia type at baseline (non-ventilated HAP vs. ventilated HAP/VAP) and 2) APACHE II score at baseline (< 15 vs. ≥ 15). A sequential testing approach was employed to control the type 1 error across the primary and the key secondary endpoint.

Missing data

Any subject missing an evaluation for a specific endpoint (clinical or microbiological) at any particular visit was considered as being "indeterminate" for that endpoint in the MITT and mMITT populations. The following were exceptions to this rule:

• Subjects discontinuing IV study therapy due to lack of efficacy (i.e., withdrawals with subsequent non-study antibiotic therapy or subjects requiring therapy beyond 21 days) were considered as "failures" with respect to clinical response at the time of discontinuation and all subsequent time points.

• Subjects discontinuing IV study therapy due to lack of efficacy were presumed to have persistence for the microbiological response at the time of discontinuation and all subsequent time points.

Since a favourable clinical response at EFU required an assessment of "cure" or "sustained cure", an assessment of "indeterminate" would be considered a failure to achieve a favourable clinical response.

Analysis populations

The MITT population was defined as all randomised subjects who receive at least one dose of IV study therapy and did not have the presence of Gram-positive cocci only on baseline Gram stain.

The mMITT population was defined as all randomised subjects who receive at least one dose of IV study therapy and do not have Gram-positive cocci only on baseline Gram stain and who have a baseline bacterial pathogen identified as the cause of HAP/VAP against which IMI/REL has been shown to have antibacterial activity.

The CE population was a subset of the MITT population who also met the following criteria:

1. Met important diagnostic criteria for entry into the study,
2. Had no significant deviation from the protocol that could impact the assessment of efficacy,
3. Received the minimum duration of IV study therapy, and
4. Had an efficacy assessment at the time point of interest.

The ME population was a subset of the CE population who also meet the following criteria:

1. Had a baseline bacterial pathogen identified as the cause of HAP/VAP against which IMI/REL has been shown to have antibacterial activity, and
2. Had results from a lower respiratory tract culture obtained at the indicated time point.

Results

Participant flow

A total of 583 participants were screened, 537 were randomised, and 535 received at least 1 dose of trial treatment (IMI/REL, 266 participants; PIP/TAZ, 269 participants). Of the 46 participants who were not randomised, 43 (93.5%) did not fulfil inclusion or exclusion criteria (screen failures) and 3 (6.5%) withdrew consent.

Table E2. Disposition of subjects

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					46	
Subjects in population	268		269		537	
Status for Trial						
Completed	185	(69.0)	187	(69.5)	372	(69.3)
Discontinued	83	(31.0)	82	(30.5)	165	(30.7)
Adverse Event	2	(0.7)	2	(0.7)	4	(0.7)
Death	44	(16.4)	58	(21.6)	102	(19.0)
Lost To Follow-Up	2	(0.7)	1	(0.4)	3	(0.6)
Non-Compliance With Protocol†	6	(2.2)	7	(2.6)	13	(2.4)
Physician Decision	1	(0.4)	1	(0.4)	2	(0.4)
Subject Moved	17	(6.3)	5	(1.9)	22	(4.1)
Withdrawal By Parent/Guardian	0	(0.0)	1	(0.4)	1	(0.2)
Withdrawal By Subject	11	(4.1)	7	(2.6)	18	(3.4)
Status for Study Medication in Trial						
Started	266		269		535	
Completed	209	(78.6)	187	(69.5)	396	(74.0)
Discontinued	57	(21.4)	82	(30.5)	139	(26.0)
ALT/AST	1	(0.4)	1	(0.4)	2	(0.4)
Adverse Event	14	(5.3)	18	(6.7)	32	(6.0)
Creatinine/EGFR	1	(0.4)	1	(0.4)	2	(0.4)
Death	12	(4.5)	14	(5.2)	26	(4.9)
Hemodialysis Discontinuation Criteria	2	(0.8)	8	(3.0)	10	(1.9)
Non-Compliance With Study Drug	1	(0.4)	1	(0.4)	2	(0.4)
Physician Decision	6	(2.3)	13	(4.8)	19	(3.6)
Protocol Violation	0	(0.0)	1	(0.4)	1	(0.2)
Treatment Failure	17	(6.4)	23	(8.6)	40	(7.5)
Withdrawal By Parent/Guardian	1	(0.4)	1	(0.4)	2	(0.4)
Withdrawal By Subject	2	(0.8)	1	(0.4)	3	(0.6)

† Encompasses subjects who completed the final visit (Day 28) prior to protocol-specified window, therefore they did not complete full participation per protocol and were considered discontinued for their final trial status.
The % is calculated based on the number of all randomized subjects.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Recruitment

The first patient´s first visit was 28 January 2016. The last patient´s last visit was 3 April 2019. The date for database lock was 22 July 2019. 120 centres in 28 countries world-wide screened at least 1 subject.

Conduct of the study

Of the major amendments made to the protocol, none would be expected to result in any favour for the IMI/REL treatment group.

A total of 675 important protocol deviations were reported for 334 participants in this study. Of these important deviations, 147 protocol deviations for 131 participants (63 participants in the IMI/REL group and

68 participants in the PIP/TAZ group) were clinically important. The incidence and types of clinically important protocol deviations were comparable in both treatment groups.

Table E3. Summary of important protocol deviation – clinically important (all randomized subjects)

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	268		269		537	
with one or more clinically important protocol deviations	63	(23.5)	68	(25.3)	131	(24.4)
with no clinically important protocol deviations	205	(76.5)	201	(74.7)	406	(75.6)
Discontinuation Criteria	0	(0.0)	1	(0.4)	1	(0.2)
Inclusion/ Exclusion Criteria	52	(19.4)	43	(16.0)	95	(17.7)
Prohibited Medications	10	(3.7)	18	(6.7)	28	(5.2)
Study Intervention	9	(3.4)	10	(3.7)	19	(3.5)
Every subject is counted a single time for each applicable row and column. The % is calculated based on the number of all randomized subjects. IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.						

Baseline data

The treatment groups were generally comparable with regards to all participant characteristics (see table below).

Table E4. Demographic and subject characteristics (MITT population)

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	264		267		531	
Gender						
Male	178	(67.4)	189	(70.8)	367	(69.1)
Female	86	(32.6)	78	(29.2)	164	(30.9)
Age (Years)						
< 65	151	(57.2)	152	(56.9)	303	(57.1)
≥ 65	113	(42.8)	115	(43.1)	228	(42.9)
Subjects with data	264		267		531	
Mean	60.5		58.8		59.6	
Race						
American Indian or Alaska Native	5	(1.9)	8	(3.0)	13	(2.4)
Asian	40	(15.2)	37	(13.9)	77	(14.5)
Black or African American	4	(1.5)	6	(2.2)	10	(1.9)
Multiple	9	(3.4)	7	(2.6)	16	(3.0)
American Indian or Alaska Native and Black or African American	1	(0.4)	0	(0.0)	1	(0.2)
American Indian or Alaska Native and White	5	(1.9)	1	(0.4)	6	(1.1)
Black or African American and White	3	(1.1)	6	(2.2)	9	(1.7)
Native Hawaiian or Other Pacific Islander	0	(0.0)	1	(0.4)	1	(0.2)
White	206	(78.0)	207	(77.5)	413	(77.8)
Missing	0	(0.0)	1	(0.4)	1	(0.2)
Region						
Americas	59	(22.3)	71	(26.6)	130	(24.5)
Europe	166	(62.9)	160	(59.9)	326	(61.4)
Asia Pacific	39	(14.8)	36	(13.5)	75	(14.1)
Height (cm)						
Subjects with data	263		267		530	
Mean	169.4		169.8		169.6	
Weight (kg)						
Subjects with data	264		267		531	
Mean	76.0		76.7		76.3	
BMI (kg/m2)						
Subjects with data	263		267		530	
Mean	26.3		26.4		26.4	
APACHE II score at baseline						
APACHE II Score < 15	139	(52.7)	140	(52.4)	279	(52.5)
APACHE II Score ≥ 15	125	(47.3)	127	(47.6)	252	(47.5)

Ventilation status at randomization						
Non-Ventilated HABP	147	(55.7)	145	(54.3)	292	(55.0)
Ventilated HABP/VABP	117	(44.3)	122	(45.7)	239	(45.0)
Pneumonia type of primary diagnosis						
Non-Ventilated HABP	142	(53.8)	131	(49.1)	273	(51.4)
Ventilated HABP/VABP	122	(46.2)	136	(50.9)	258	(48.6)
Ventilated HABP	31	(11.7)	35	(13.1)	66	(12.4)
VABP	91	(34.5)	101	(37.8)	192	(36.2)
Days in current hospital admission before randomization						
Subjects with data	264		266		530	
Mean	30.4		31.1		30.7	
Admitted in ICU at randomization						
Yes	175	(66.3)	176	(65.9)	351	(66.1)
No	89	(33.7)	91	(34.1)	180	(33.9)
CPIS score						
< 6	114	(43.2)	95	(35.6)	209	(39.4)
≥ 6	150	(56.8)	172	(64.4)	322	(60.6)
Subjects with data	264		267		531	
Mean	5.9		6.1		6.0	

Concurrent bacteremia with any pathogen						
Yes	15	(5.7)	16	(6.0)	31	(5.8)
No	249	(94.3)	251	(94.0)	500	(94.2)
Concurrent bacteremia with baseline LRT pathogens						
Yes	5	(1.9)	7	(2.6)	12	(2.3)
No	259	(98.1)	260	(97.4)	519	(97.7)
ALT or AST > ULN at randomization						
Y	71	(26.9)	91	(34.1)	162	(30.5)
N	178	(67.4)	161	(60.3)	339	(63.8)
Missing	15	(5.7)	15	(5.6)	30	(5.6)
Stage of renal impairment based on baseline creatinine clearance (mL/min)						
Normal (≥ 90)	141	(53.4)	135	(50.6)	276	(52.0)
Mild (< 90 to ≥ 60)	52	(19.7)	72	(27.0)	124	(23.4)
Moderate (< 60 to ≥ 30)	61	(23.1)	48	(18.0)	109	(20.5)
Severe (< 30 to ≥ 15)	10	(3.8)	12	(4.5)	22	(4.1)
Number of baseline LRT pathogens						
Monomicrobial	160	(60.6)	160	(59.9)	320	(60.3)
Polymicrobial	55	(20.8)	58	(21.7)	113	(21.3)
None	49	(18.6)	49	(18.4)	98	(18.5)
Baseline LRT specimen collection method						
Bronchoalveolar Lavage	47	(17.8)	53	(19.9)	100	(18.8)
Mini-Bronchoalveolar Lavage	54	(20.5)	56	(21.0)	110	(20.7)
Protected-Brush Sampling	6	(2.3)	8	(3.0)	14	(2.6)
Endotracheal Tube Aspiration	71	(26.9)	70	(26.2)	141	(26.6)
Transtracheal Aspiration	24	(9.1)	22	(8.2)	46	(8.7)
Sputum	58	(22.0)	57	(21.3)	115	(21.7)
Missing	4	(1.5)	3	(1.1)	7	(1.3)

BMI = body mass index; APACHE = acute physiologic assessment and chronic health evaluation; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia; ICU = intensive care unit; CPIS = clinical pulmonary infection score; LRT = lower respiratory tract; ALT = alanine transaminase; AST = aspartate aminotransferase; ULN = upper limit of normal.

IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Baseline microbiology

LRT cultures

Aerobic gram-negative bacilli were predominant in both treatment groups, and the most frequently isolated was *K. pneumoniae*. *P. aeruginosa* was the next most common pathogen. The distribution of pathogens in both treatment groups was generally comparable, with the exception of *P. aeruginosa*, which was isolated from a lower proportion of participants in the IMI/REL group compared with PIP/TAZ. Differences between the groups for other key pathogens were <5.0%.

Table E5. Baseline pathogens from LRT cultures (mMITT population)

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population, N	215		218		433	
Aerobic gram-negative bacillus	**192**	**(89.3)**	**194**	**(89.0)**	**386**	**(89.1)**
Achromobacter	1	(0.5)	0	(0.0)	1	(0.2)
Achromobacter xylosoxidans	0	(0.0)	1	(0.5)	1	(0.2)
Acinetobacter	1	(0.5)	0	(0.0)	1	(0.2)
Acinetobacter calcoaceticus-baumannii complex	32	(14.9)	36	(16.5)	68	(15.7)
Acinetobacter haemolyticus	2	(0.9)	0	(0.0)	2	(0.5)
Acinetobacter lwoffii	1	(0.5)	0	(0.0)	1	(0.2)
Acinetobacter pitii	3	(1.4)	1	(0.5)	4	(0.9)
Acinetobacter ursingii	1	(0.5)	1	(0.5)	2	(0.5)
Citrobacter freundii	2	(0.9)	3	(1.4)	5	(1.2)
Citrobacter koseri	1	(0.5)	5	(2.3)	6	(1.4)
Enterobacter	1	(0.5)	0	(0.0)	1	(0.2)
Enterobacter asburiae	3	(1.4)	2	(0.9)	5	(1.2)
Enterobacter cloacae	8	(3.7)	19	(8.7)	27	(6.2)
Escherichia coli	30	(14.0)	37	(17.0)	67	(15.5)
Klebsiella aerogenes	5	(2.3)	4	(1.8)	9	(2.1)
Klebsiella oxytoca	2	(0.9)	2	(0.9)	4	(0.9)
Klebsiella pneumoniae	58	(27.0)	53	(24.3)	111	(25.6)
Klebsiella variicola	2	(0.9)	2	(0.9)	4	(0.9)
Leclercia adecarboxylata	0	(0.0)	1	(0.5)	1	(0.2)
Moraxella catarrhalis	3	(1.4)	1	(0.5)	4	(0.9)
Morganella morganii	0	(0.0)	2	(0.9)	2	(0.5)
Proteus hauseri	2	(0.9)	0	(0.0)	2	(0.5)
Proteus mirabilis	6	(2.8)	5	(2.3)	11	(2.5)
Proteus penneri	1	(0.5)	0	(0.0)	1	(0.2)
Proteus vulgaris	1	(0.5)	0	(0.0)	1	(0.2)
Providencia rettgeri	0	(0.0)	1	(0.5)	1	(0.2)
Providencia stuartii	1	(0.5)	0	(0.0)	1	(0.2)
Pseudomonas aeruginosa	34	(15.8)	48	(22.0)	82	(18.9)
Pseudomonas monteilii	1	(0.5)	1	(0.5)	2	(0.5)
Raoultella ornithinolytica	2	(0.9)	1	(0.5)	3	(0.7)
Serratia marcescens	13	(6.0)	4	(1.8)	17	(3.9)
Aerobic gram-negative coccobacillus	**13**	**(6.0)**	**14**	**(6.4)**	**27**	**(6.2)**
Haemophilus influenzae	13	(6.0)	12	(5.5)	25	(5.8)
Haemophilus parainfluenzae	0	(0.0)	2	(0.9)	2	(0.5)

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Aerobic gram-negative coccus	**2**	**(0.9)**	**0**	**(0.0)**	**2**	**(0.5)**
Neisseria subflava	2	(0.9)	0	(0.0)	2	(0.5)
Aerobic gram-positive bacillus	**2**	**(0.9)**	**0**	**(0.0)**	**2**	**(0.5)**
Bacillus cereus	1	(0.5)	0	(0.0)	1	(0.2)
Corynebacterium striatum	1	(0.5)	0	(0.0)	1	(0.2)
Aerobic gram-positive coccus	**45**	**(20.9)**	**40**	**(18.3)**	**85**	**(19.6)**
Enterococcus durans	2	(0.9)	0	(0.0)	2	(0.5)
Enterococcus faecalis	3	(1.4)	4	(1.8)	7	(1.6)
Methicillin susceptible staphylococcus aureus	23	(10.7)	22	(10.1)	45	(10.4)
Staphylococcus aureus	1	(0.5)	1	(0.5)	2	(0.5)
Staphylococcus epidermidis	1	(0.5)	1	(0.5)	2	(0.5)
Staphylococcus haemolyticus	3	(1.4)	0	(0.0)	3	(0.7)
Staphylococcus hominis	1	(0.5)	0	(0.0)	1	(0.2)
Staphylococcus lugdunensis	0	(0.0)	1	(0.5)	1	(0.2)
Staphylococcus simulans	1	(0.5)	0	(0.0)	1	(0.2)
Staphylococcus xylosus	1	(0.5)	0	(0.0)	1	(0.2)
Streptococcus agalactiae	2	(0.9)	2	(0.9)	4	(0.9)
Streptococcus mitis group	1	(0.5)	3	(1.4)	4	(0.9)
Streptococcus oralis	1	(0.5)	0	(0.0)	1	(0.2)
Streptococcus parasanguinis	1	(0.5)	1	(0.5)	2	(0.5)
Streptococcus pneumoniae	5	(2.3)	5	(2.3)	10	(2.3)
Streptococcus vestibularis	0	(0.0)	1	(0.5)	1	(0.2)
Anaerobic gram-positive coccus	**0**	**(0.0)**	**3**	**(1.4)**	**3**	**(0.7)**
Streptococcus anginosus	0	(0.0)	1	(0.5)	1	(0.2)
Streptococcus constellatus	0	(0.0)	2	(0.9)	2	(0.5)

N = number of microbiological modified intent-to-treat subjects.
n = number of subjects with at least one of the specific baseline pathogen.
%=100(n/N).
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Table E6. Susceptibility to study drug of key baseline pathogens from LRT culture based on EUCAST MIC breakpoints (mMITT population)

	Susceptibility to IMI/REL Treatment Group: IMI/REL (N=215)							Susceptibility to PIP/TAZ Treatment Group: PIP/TAZ (N=218)						
	Total			S		R		Total			S		R	
	N1	n	M	m	(%)	m	(%)	N1	n	M	m	(%)	m	(%)
All Pathogens	171	200	200	164	(82.0)	36	(18.0)	193	226	182	125	(68.7)	57	(31.3)
Aerobic Gram-Negative Bacillus	162	186	186	152	(81.7)	34	(18.3)	183	214	170	125	(73.5)	45	(26.5)
Acinetobacter calcoaceticus-baumannii complex	32	32	32	4	(12.5)	28	(87.5)	36	37	0	0	(0.0)	0	(0.0)
Citrobacter freundii	2	2	2	2	(100.0)	0	(0.0)	3	3	3	1	(33.3)	2	(66.7)
Citrobacter koseri	1	1	1	1	(100.0)	0	(0.0)	5	5	5	5	(100.0)	0	(0.0)
Enterobacter cloacae	8	8	8	8	(100.0)	0	(0.0)	19	19	19	16	(84.2)	3	(15.8)
Escherichia coli	30	30	30	30	(100.0)	0	(0.0)	37	37	35	30	(85.7)	5	(14.3)
Klebsiella aerogenes	5	5	5	5	(100.0)	0	(0.0)	4	4	4	3	(75.0)	1	(25.0)
Klebsiella oxytoca	2	2	2	2	(100.0)	0	(0.0)	2	2	2	2	(100.0)	0	(0.0)
Klebsiella pneumoniae	58	58	58	57	(98.3)	1	(1.7)	53	53	48	30	(62.5)	18	(37.5)
Pseudomonas aeruginosa	34	35	35	31	(88.6)	4	(11.4)	48	50	50	34	(68.0)	16	(32.0)
Serratia marcescens	13	13	13	12	(92.3)	1	(7.7)	4	4	4	4	(100.0)	0	(0.0)
Aerobic Gram-Negative Coccobacillus	13	14	14	12	(85.7)	2	(14.3)	12	12	12	0	(0.0)	12	(100.0)
Haemophilus influenzae	13	14	14	12	(85.7)	2	(14.3)	12	12	12	0	(0.0)	12	(100.0)

N = number of microbiological modified intent-to-treat subjects, N1 = number of subjects with the pathogen, n = number of pathogens.
M = number of pathogens with susceptibility interpretations (S, R) based on EUCAST, m = number of pathogens with the corresponding susceptibility interpretation, % = (m/M) x 100.
S = Susceptible, R = Resistant; EUCAST = European Committee on Antimicrobial Susceptibility Testing; LRT = lower respiratory tract.
Susceptibility interpretation by broth microdilution testing for PIP/TAZ was based on the European Committee on Antimicrobial Susceptibility Testing breakpoint tables for interpretation of MICs, Version 9.0. imipenem/REL susceptibility was determined using the provisional EUCAST breakpoints. For organisms without imipenem/REL breakpoints, imipenem interpretive criteria were applied to determine imipenem/REL susceptibility.
IMI/REL = imipenem/cilastatin/relebactam for treatment group and imipenem/relebactam for susceptibility testing; PIP/TAZ = piperacillin/tazobactam.

Blood cultures

There were few baseline blood pathogens (table below).

Table E7. Baseline pathogens from blood cultures (mMITT population)

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population, N	215		218		433	
Aerobic gram-negative bacillus	**5**	**(2.3)**	**9**	**(4.1)**	**14**	**(3.2)**
Acinetobacter calcoaceticus-baumannii complex	1	(0.5)	2	(0.9)	3	(0.7)
Enterobacter cloacae	1	(0.5)	1	(0.5)	2	(0.5)
Escherichia coli	1	(0.5)	1	(0.5)	2	(0.5)
Klebsiella pneumoniae	1	(0.5)	4	(1.8)	5	(1.2)
Proteus mirabilis	1	(0.5)	0	(0.0)	1	(0.2)
Pseudomonas aeruginosa	0	(0.0)	1	(0.5)	1	(0.2)
Aerobic gram-positive coccus	**7**	**(3.3)**	**5**	**(2.3)**	**12**	**(2.8)**
Coagulase negative staphylococci	1	(0.5)	0	(0.0)	1	(0.2)
Methicillin susceptible staphylococcus aureus	3	(1.4)	1	(0.5)	4	(0.9)
Staphylococcus capitis	0	(0.0)	1	(0.5)	1	(0.2)
Staphylococcus epidermidis	3	(1.4)	2	(0.9)	5	(1.2)
Staphylococcus hominis	0	(0.0)	1	(0.5)	1	(0.2)
Streptococcus oralis	1	(0.5)	0	(0.0)	1	(0.2)

N = number of microbiological modified intent-to-treat subjects.
n = number of subjects with at least one of the specific baseline pathogen.
%=100(n/N).
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Compliance and exposure to study drug

Given that participants were hospitalised for IV administration of trial treatment, compliance with the trial treatment regimen was very high in both treatment groups. The mean duration of trial treatment was 8.7 and 8.3 days for the IMI/REL and PIP/TAZ groups, respectively.

Prior and concomitant exposure to other antibiotics

Most participants (86.3% of MITT population) received non-trial systemic anti-infective medications prior to trial treatment. The most frequently reported (≥10% overall) prior anti-infective medications were ceftriaxone (20.2%), piperacillin sodium/tazobactam sodium (19.0%), metronidazole (11.1%), vancomycin (10.4%), and levofloxacin (10.0%). Use of these medications was generally comparable in both treatment groups.

The most frequently reported (≥10% overall) concomitant anti-infective medications were linezolid (97.6%), piperacillin sodium/tazobactam sodium (17.9%), meropenem (14.9%), and vancomycin (10. 7%). Notably, approximately 10% of participants received colistin or polymyxins. Use of concomitant anti-infective agents was generally comparable in both treatment groups.

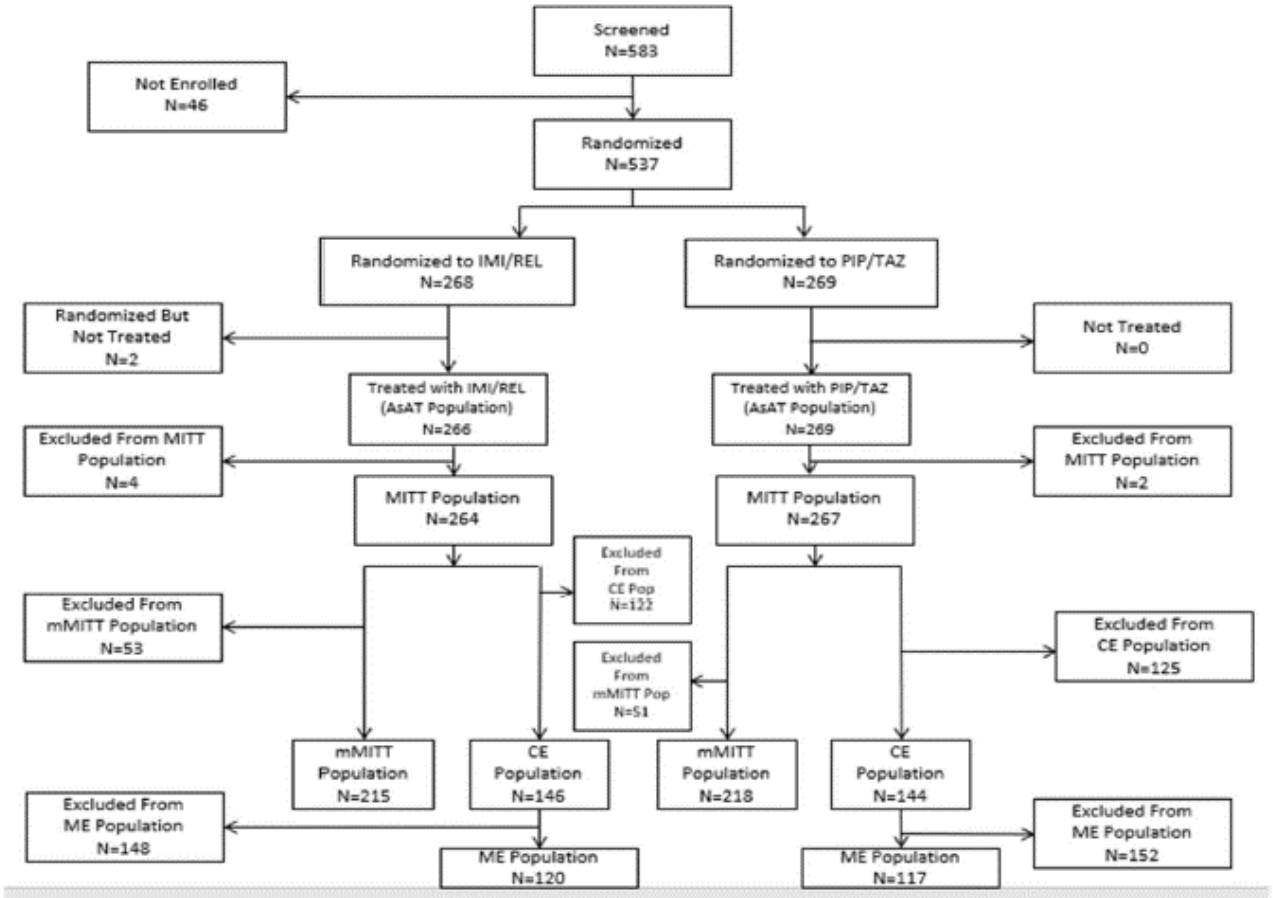
Numbers analysed

Six randomised participants were excluded from the MITT population because they were either not treated (two subjects in the IMI/REL treatment group; one subject because of adverse event and one subject because of physician decision), had a Gram stain result showing only gram-positive cocci (two subjects in the IMI/REL treatment group and one subject in the PIP/TAZ treatment group), or were missing a microscopy result at screening (one subject in the PIP/TAZ treatment group).

In the mMITT population, 98 additional subjects (49 in each treatment group) were excluded from the MITT population because baseline LRT specimen did not meet culture and identification requirements for inclusion in mMITT.

The most common reasons for exclusion from the CE population were prior antibacterial violation (34 vs. 33 subjects), protocol specified minimum duration of study drug not received (30 vs. 45 subjects) and confounding antibacterial post-treatment (32 vs 25 subjects).

Figure E1. Schematic of analysis populations



Outcomes and estimation

Primary and key secondary analyses

IMI/REL was non-inferior to PIP/TAZ in participants with HAP/VAP, as assessed by the incidence rate of favourable clinical response at the EFU visit in the MITT population. Among participants allocated to randomisation strata with baseline APACHE II ≥15 in the MITT population, those treated with IMI/REL had a numerically higher favourable clinical response at the EFU visit compared to PIP/TAZ, regardless of ventilation status (table below).

Table E8. Proportion of subjects achieving favourable clinical response at EFU including by randomisation stratum (MITT population)

	IMI/REL		PIP/TAZ		Unadjusted Difference	Adjusted Difference		P-value
Visit	n/m	(%)	n/m	(%)	%	%	(CI)	
EFU	161/264	(61.0)	149/267	(55.8)	5.2	5.0	(-3.2, 13.2)‡ (-4.4, 14.4)§	p‡ <0.001 p§ =0.235
Non-Ventilated HABP with Baseline APACHE II < 15	70/102	(68.6)	74/102	(72.5)	-3.9			
Non-Ventilated HABP with Baseline APACHE II ≥ 15	27/45	(60.0)	20/43	(46.5)	13.5			
Ventilated HABP/VABP with Baseline APACHE II < 15	22/41	(53.7)	24/41	(58.5)	-4.9			
Ventilated HABP/VABP with Baseline APACHE II ≥ 15	42/76	(55.3)	31/81	(38.3)	17.0			

Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by randomization stratum.
† 95% CI.
‡ The 95% CI and the P-value are for the non-inferiority hypothesis test where the non-inferiority margin is -12.5% and alpha level (one sided) is 0.025.
§ The 97.5% CI and the P-value are for the superiority hypothesis test where the alpha level (two sided) is 0.025.
n/m = number of subjects with favorable clinical response / number of modified intent-to-treat subjects who should have clinical response assessed at the corresponding visit.
OTX1 = on-therapy visit 1; OTX2 = on-therapy visit 2; OTX3 = on-therapy visit 3; EOT = end of therapy; EFU = early follow-up; Day 28 = day 28 post-randomization.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

IMI/REL was also non-inferior to PIP/TAZ in participants with HAP/VAP, as assessed by the incidence rate of all-cause mortality through Day 28 in the MITT population. Among participants allocated to either strata with APACHE II ≥15, those treated with IMI/REL had a numerically lower rate of all-cause mortality through Day 28 compared to those treated with PIP/TAZ, regardless of ventilation status (table below).

Table E9. Incidence of all-cause mortality at day 28 and by randomisation stratum (MITT population)

	IMI/REL		PIP/TAZ		Unadjusted Difference	Adjusted Difference		P-value
Visit	n/m	(%)	n/m	(%)	%	%	(CI)	
Subjects in population	264		267					
Day 28	42/264	(15.9)	57/267	(21.3)	-5.4	-5.3	(-11.9, 1.2)‡ (-12.9, 2.1)§	p‡ <0.001 p§ =0.111
Non-Ventilated HABP with Baseline APACHE II < 15	10/102	(9.8)	6/102	(5.9)	3.9			
Non-Ventilated HABP with Baseline APACHE II ≥ 15	7/45	(15.6)	12/43	(27.9)	-12.4			
Ventilated HABP/VABP with Baseline APACHE II < 15	10/41	(24.4)	7/41	(17.1)	7.3			
Ventilated HABP/VABP with Baseline APACHE II ≥ 15	15/76	(19.7)	32/81	(39.5)	-19.8			

Adjusted differences and the corresponding confidence intervals are based on Miettinen & Nurminen method stratified by randomization stratum.
† 95% CI.
‡ The 95% CI and the P-value are for the non-inferiority hypothesis test where the non-inferiority margin is 10% and alpha level (one sided) is 0.025.
§ The 97.5% CI and the P-value are for the superiority hypothesis test where the alpha level (two sided) is 0.025.
n/m = number of subjects with survival status of death or unknown / number of modified intent-to-treat subjects.
EFU = early follow-up; Day 28 = day 28 post-randomization.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Neither of the primary endpoint or key secondary endpoint met the success criteria for the superiority hypotheses.

Ancillary analyses

Other secondary analyses

In the mMITT population, the incidence rate of all-cause mortality through Day 28 was essentially comparable in both treatment groups and consistent with the primary efficacy analysis results observed for the MITT population. In the MITT and mMITT populations, the incidence rate of all-cause mortality at the EFU visit was furthermore comparable in both treatment groups and similar to the incidence rates observed at Day 28 (data not shown).

The proportion of participants with favourable clinical response at the EFU visit in the CE population was essentially similar in the treatment groups (table below).

Table E10. Proportion of subjects achieving favourable clinical response at EFU (CE population)

	IMI/REL		PIP/TAZ		Unadjusted Difference	Adjusted Difference	
Visit	n/m	(%)	n/m	(%)	%	%	(95% CI)‡
CE population at EFU	147		144				
EFU	101/136	(74.3)	100/126	(79.4)	-5.1	-3.7	(-13.6, 6.4)

‡ Adjusted differences and 95% confidence intervals are based on Miettinen & Nurminen method stratified by randomization stratum.

n/m = number of subjects with a favorable clinical response / number of clinically-evaluable subjects who should have clinical response assessed at the corresponding visit with non-missing/non-indeterminate response.

OTX1 = on-therapy visit 1; OTX2 = on-therapy visit 2; OTX3 = on-therapy visit 3; EOT = end of therapy; EFU = early follow-up; Day 28 = day 28 post-randomization.

IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

In the mMITT and ME populations, the proportion of participants achieving favourable overall microbiological response rates were comparable in both treatment groups at the EFU visit (data not shown).

Efficacy analyses by baseline pathogen from LRT culture

Table E11. Proportion of subjects achieving favourable clinical response at EFU by baseline pathogen from LRT culture (mMITT population)

	IMI/REL		PIP/TAZ		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[‡]
Subjects in population	215		218			
Aerobic gram-negative bacillus						
Achromobacter	0/1	(0.0)	0/0			
Achromobacter xylosoxidans	0/0		0/1	(0.0)		
Acinetobacter	1/1	(100.0)	0/0			
Acinetobacter calcoaceticus-baumannii complex	19/32	(59.4)	21/36	(58.3)	1.0	(-22.1, 23.9)
Acinetobacter haemolyticus	2/2	(100.0)	0/0			
Acinetobacter lwoffii	1/1	(100.0)	0/0			
Acinetobacter pitii	3/3	(100.0)	0/1	(0.0)	100.0	
Acinetobacter ursingii	0/1	(0.0)	0/1	(0.0)	0.0	
Citrobacter freundii	1/2	(50.0)	2/3	(66.7)	-16.7	
Citrobacter koseri	1/1	(100.0)	2/5	(40.0)	60.0	
Enterobacter	1/1	(100.0)	0/0			
Enterobacter asburiae	2/3	(66.7)	1/2	(50.0)	16.7	
Enterobacter cloacae	6/8	(75.0)	13/19	(68.4)	6.6	(-33.4, 38.0)
Escherichia coli	18/30	(60.0)	21/37	(56.8)	3.2	(-20.4, 26.2)
Klebsiella aerogenes	4/5	(80.0)	2/4	(50.0)	30.0	(-32.9, 75.8)
Klebsiella oxytoca	1/2	(50.0)	2/2	(100.0)	-50.0	
Klebsiella pneumoniae	34/58	(58.6)	32/53	(60.4)	-1.8	(-19.7, 16.4)
Klebsiella variicola	1/2	(50.0)	1/2	(50.0)	0.0	
Leclercia adecarboxylata	0/0		1/1	(100.0)		
Moraxella catarrhalis	2/3	(66.7)	1/1	(100.0)	-33.3	
Morganella morganii	0/0		0/2	(0.0)		
Proteus hauseri	2/2	(100.0)	0/0			
Proteus mirabilis	3/6	(50.0)	4/5	(80.0)	-30.0	(-71.6, 28.8)
Proteus penneri	0/1	(0.0)	0/0			
Proteus vulgaris	1/1	(100.0)	0/0			
Providencia rettgeri	0/0		0/1	(0.0)		
Providencia stuartii	0/1	(0.0)	0/0			
Pseudomonas aeruginosa	14/34	(41.2)	29/48	(60.4)	-19.2	(-39.5, 2.8)
Pseudomonas monteilii	1/1	(100.0)	0/1	(0.0)	100.0	
Raoultella ornithinolytica	2/2	(100.0)	0/1	(0.0)	100.0	
Serratia marcescens	9/13	(69.2)	3/4	(75.0)	-5.8	(-44.1, 46.7)
Aerobic gram-negative coccobacillus						
Haemophilus influenzae	9/13	(69.2)	8/12	(66.7)	2.6	(-33.2, 38.3)
Haemophilus parainfluenzae	0/0		0/2	(0.0)		

	IMI/REL		PIP/TAZ		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)‡
Aerobic gram-negative coccus						
Neisseria subflava	2/2	(100.0)	0/0			
Aerobic gram-positive bacillus						
Bacillus cereus	1/1	(100.0)	0/0			
Corynebacterium striatum	0/1	(0.0)	0/0			
Aerobic gram-positive coccus						
Enterococcus durans	2/2	(100.0)	0/0			
Enterococcus faecalis	0/3	(0.0)	3/4	(75.0)	-75.0	
Methicillin susceptible staphylococcus aureus	9/23	(39.1)	13/22	(59.1)	-20.0	(-46.2, 9.5)
Staphylococcus aureus	1/1	(100.0)	1/1	(100.0)	0.0	
Staphylococcus epidermidis	1/1	(100.0)	0/1	(0.0)	100.0	
Staphylococcus haemolyticus	2/3	(66.7)	0/0			
Staphylococcus hominis	1/1	(100.0)	0/0			
Staphylococcus lugdunensis	0/0		0/1	(0.0)		
Staphylococcus simulans	1/1	(100.0)	0/0			
Staphylococcus xylosus	1/1	(100.0)	0/0			
Streptococcus agalactiae	1/2	(50.0)	1/2	(50.0)	0.0	
Streptococcus mitis group	1/1	(100.0)	1/3	(33.3)	66.7	
Streptococcus oralis	0/1	(0.0)	0/0			
Streptococcus parasanguinis	0/1	(0.0)	1/1	(100.0)	-100.0	
Streptococcus pneumoniae	4/5	(80.0)	4/5	(80.0)	0.0	(-51.7, 51.7)
Streptococcus vestibularis	0/0		1/1	(100.0)		
Anaerobic gram-positive coccus						
Streptococcus anginosus	0/0		1/1	(100.0)		
Streptococcus constellatus	0/0		2/2	(100.0)		

‡Differences and corresponding 95% confidence intervals are based on Miettinen & Nurminen method and confidence interval will not be presented for m less than 4.

n/m = the number of subjects with a favorable clinical response within each category / the number of microbiological modified intent-to-treat subjects who have the corresponding baseline pathogen from LRT culture.

IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Table E12. Proportion of subjects achieving favourable per-pathogen microbiological response at EFU by baseline pathogen from LRT culture (mMITT population)

	IMI/REL		PIP/TAZ		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[1]
Subjects in population	215		218			
Aerobic gram-negative bacillus						
Achromobacter	0/1	(0.0)	0/0			
Achromobacter xylosoxidans	0/0		1/1	(100.0)		
Acinetobacter	0/1	(0.0)	0/0			
Acinetobacter calcoaceticus-baumannii complex	24/32	(75.0)	23/36	(63.9)	11.1	(-11.2, 32.1)
Acinetobacter haemolyticus	2/2	(100.0)	0/0			
Acinetobacter lwoffii	1/1	(100.0)	0/0			
Acinetobacter pitii	2/3	(66.7)	0/1	(0.0)	66.7	
Acinetobacter ursingii	0/1	(0.0)	0/1	(0.0)	0.0	
Citrobacter freundii	2/2	(100.0)	3/3	(100.0)	0.0	
Citrobacter koseri	1/1	(100.0)	2/5	(40.0)	60.0	
Enterobacter	1/1	(100.0)	0/0			
Enterobacter asburiae	2/3	(66.7)	0/2	(0.0)	66.7	
Enterobacter cloacae	6/8	(75.0)	13/19	(68.4)	6.6	(-33.4, 38.0)
Escherichia coli	20/30	(66.7)	22/37	(59.5)	7.2	(-16.2, 29.4)
Klebsiella aerogenes	4/5	(80.0)	3/4	(75.0)	5.0	(-49.6, 59.8)
Klebsiella oxytoca	1/2	(50.0)	2/2	(100.0)	-50.0	
Klebsiella pneumoniae	38/58	(65.5)	34/53	(64.2)	1.4	(-16.3, 19.1)
Klebsiella variicola	1/2	(50.0)	1/2	(50.0)	0.0	
Leclercia adecarboxylata	0/0		1/1	(100.0)		
Moraxella catarrhalis	2/3	(66.7)	1/1	(100.0)	-33.3	
Morganella morganii	0/0		0/2	(0.0)		
Proteus hauseri	2/2	(100.0)	0/0			
Proteus mirabilis	3/6	(50.0)	4/5	(80.0)	-30.0	(-71.6, 28.8)
Proteus penneri	1/1	(100.0)	0/0			
Proteus vulgaris	1/1	(100.0)	0/0			
Providencia rettgeri	0/0		0/1	(0.0)		
Providencia stuartii	1/1	(100.0)	0/0			
Pseudomonas aeruginosa	17/34	(50.0)	29/48	(60.4)	-10.4	(-31.4, 11.3)
Pseudomonas monteilii	1/1	(100.0)	0/1	(0.0)	100.0	
Raoultella ornithinolytica	2/2	(100.0)	0/1	(0.0)	100.0	
Serratia marcescens	9/13	(69.2)	1/4	(25.0)	44.2	(-11.1, 76.6)
Aerobic gram-negative coccobacillus						
Haemophilus influenzae	9/13	(69.2)	9/12	(75.0)	-5.8	(-39.8, 30.1)
Haemophilus parainfluenzae	0/0		0/2	(0.0)		

	IMI/REL		PIP/TAZ		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)‡
Aerobic gram-negative coccus						
Neisseria subflava	2/2	(100.0)	0/0			
Aerobic gram-positive bacillus						
Bacillus cereus	1/1	(100.0)	0/0			
Corynebacterium striatum	0/1	(0.0)	0/0			
Aerobic gram-positive coccus						
Enterococcus durans	2/2	(100.0)	0/0			
Enterococcus faecalis	1/3	(33.3)	3/4	(75.0)	-41.7	
Methicillin susceptible staphylococcus aureus	13/23	(56.5)	14/22	(63.6)	-7.1	(-34.4, 21.3)
Staphylococcus aureus	1/1	(100.0)	1/1	(100.0)	0.0	
Staphylococcus epidermidis	1/1	(100.0)	0/1	(0.0)	100.0	
Staphylococcus haemolyticus	2/3	(66.7)	0/0			
Staphylococcus hominis	1/1	(100.0)	0/0			
Staphylococcus lugdunensis	0/0		0/1	(0.0)		
Staphylococcus simulans	1/1	(100.0)	0/0			
Staphylococcus xylosus	1/1	(100.0)	0/0			
Streptococcus agalactiae	2/2	(100.0)	1/2	(50.0)	50.0	
Streptococcus mitis group	1/1	(100.0)	2/3	(66.7)	33.3	
Streptococcus oralis	1/1	(100.0)	0/0			
Streptococcus parasanguinis	0/1	(0.0)	1/1	(100.0)	-100.0	
Streptococcus pneumoniae	3/5	(60.0)	3/5	(60.0)	0.0	(-54.4, 54.4)
Streptococcus vestibularis	0/0		1/1	(100.0)		
Anaerobic gram-positive coccus						
Streptococcus anginosus	0/0		1/1	(100.0)		
Streptococcus constellatus	0/0		2/2	(100.0)		

‡Differences and corresponding 95% confidence intervals are based on Miettinen & Nurminen method and confidence interval will not be presented for m less than 4.

n/m = the number of subjects with a favorable per-pathogen microbiological response within each category / the number of microbiological modified intent-to-treat subjects who have the corresponding baseline pathogen from LRT culture.

IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Subgroup analyses

Across most of the pre-defined subgroups (by gender, race, age below and above 65, region, ventilation status at randomisation, pneumonia type, APACHE II score below or above 15, CPIS score below or above 6, concurrent bacteraemia), essentially similar incidence rates for favourable clinical response at the EFU visit and all-cause mortality through Day 28 were observed for both treatment groups, consistent with the results of the primary and key secondary efficacy analyses (data not shown).

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial P014

Title: A Phase III, randomized, double-blind, active comparator-controlled clinical trial to study the safety, tolerability, and efficacy of imipenem/cilastatin/relebactam (MK-7655A) versus piperacillin/tazobactam in subjects with hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia			
Study identifier	Protocol number: P014MK7655A; EudraCT: 2015-000246-34		
Design	P014 (also known as MK-7655A-014 or RESTORE-IMI 2) was a phase 3 randomised, double-blind, active comparator trial to evaluate the safety, tolerability, and efficacy of IMI/REL versus PIP/TAZ in hospitalised participants with HAP/VAP.		
	Duration of main phase:		Approximately four weeks
Hypothesis	Non-inferiority		
Treatments groups	IMI/REL		Imipenem/cilastatin/relebactam 500/500/250 mg IV q6h for 7 to 14 days; Numbers randomised: 268
	PIP/TAZ		Piperacillin/tazobactam 4000/500 mg q6h for 7 to 14 days; Numbers randomised: 269
Endpoints and definitions	Primary endpoint	Favourable clinical response at the EFU visit in the MITT population	A favourable clinical response is defined as cure, i.e. all pre-therapy signs and symptoms of the index infection have resolved (or returned to "pre-infection status") AND no additional antibiotic therapy is required for the index infection
	Key secondary endpoint	All-cause mortality through Day 28 in the MITT population	Incidence of death by any cause through day 28
	Other secondary endpoint	Favourable clinical response at the EFU visit in the CE population	A favourable clinical response is defined as cure, i.e. all pre-therapy signs and symptoms of the index infection have resolved (or returned to "pre-infection status") AND no additional antibiotic therapy is required for the index infection
Database lock	22 July 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	MITT=all randomised subjects who receive at least one dose of IV study therapy and did not have the presence of Gram-positive cocci only on baseline Gram stain. EFU= early follow-up visit 7 to 14 days after the end of therapy		
Descriptive statistics and estimate variability	Treatment group	IMI/REL	PIP/TAZ
	Number of subjects	264	267
	Favourable clinical response at the EFU visit in the MITT population (%)	161 (61.0)	149 (55.8)
	Adjusted difference in % (IMI/REL vs PIP/TAZ) (95% CI)	5.0 (-3.2, 13.2)	
Analysis description	**Key Secondary Analysis**		
Analysis population and time point description	MITT=all randomised subjects who receive at least one dose of IV study therapy and did not have the presence of Gram-positive cocci only on baseline Gram stain. Through day 28		
Descriptive statistics and estimate variability	Treatment group	IMI/REL	PIP/TAZ
	Number of subjects	264	267

	All-cause mortality through Day 28 in the MITT population (%)	42 (15.9)	57 (21.3)
	Adjusted difference in % (IMI/REL vs PIP/TAZ) (95% CI)	-5.3 (-11.9, 1.2)	
Analysis description	**Other Secondary Analysis**		
Analysis population and time point description	CE=clinically evaluable i.e. a subset of the MITT population who also met the following criteria: 1. Met important diagnostic criteria for entry into the study, 2. Had no significant deviation from the protocol that could impact the assessment of efficacy, 3. Received the minimum duration of IV study therapy, and 4. Had an efficacy assessment at the time point of interest. EFU= early follow-up visit 7 to 14 days after the end of therapy		
Descriptive statistics and estimate variability	Treatment group	IMI/REL	PIP/TAZ
	Number of subjects	147	144
	Favourable clinical response at the EFU visit in the CE population	101/136*	100/126*
	Adjusted difference in % (IMI/REL vs PIP/TAZ) (95% CI)	-3.7 (-13.6, 6.4)	
Notes	* n/m = number of subjects with a favourable clinical response / number of clinically evaluable subjects who should have clinical response assessed at the corresponding visit with non-missing/non-indeterminate response		

Additional justification for SmPC updates

The MAH proposes to delete the following paragraph from section 4.4 of the SmPC:

> *Neutropenic patients and patients with very severe infections*
>
> *The recommended doses of Recarbrio may not be optimal to treat i) patients with neutropenia or ii) patients with very severe infections. Consideration should be given to using alternative therapies for these patients.*

The statement was requested by the CHMP to be included in the Recarbrio SmPC section 4.4 because of the recommendation in the Tienam SmPC section 4.2 *"It is recommended that (..) very severe infections (e.g. in neutropenic patients with a fever) should be treated with 1000 mg/1000 mg administered every 6 hours"* (see Recarbrio EPAR, Procedure No. EMEA/H/C/004808/0000 and Tienam Art. 30 referral, Procedure NO. EMEA/H/A-30/1187).

As the amount of IMI in Recarbrio is less than 1000 mg the CHMP was of the opinion that the doses recommended in the Recarbio SmPC may not be sufficient in the mentioned situations related to optimising the PK/PD and that the wording should be aligned with the Tienam SmPC although placed in section 4.4 and not 4.2. Furthermore, the dose of REL to protect 1000 mg of imipenem from hydrolysis by relevant betalactamases is unknown.

In summary, the MAH considers deletion of the paragraph in the SmPC regarding use in neutropenic patients and patients with very severe infections is warranted for the following reasons:

1. the 500/500/250 mg dose of IMI/REL is supported by robust PTA analyses and susceptibility data which demonstrate a significantly improved susceptibility profile of bacterial isolates to the combination of imipenem and REL relative to that of imipenem alone, including compared to

susceptibility rates for the higher breakpoint of 4 mg/L imipenem linked to the increased exposure dose (1000 mg/1000mg) for IMI;

2. the EUCAST expert panel of PK/PD, microbiology and clinical medicine experts approved breakpoints in accordance with the 500/500/250 mg RECARBRIO dose without "susceptible, increased exposure" or "special situations" categories for patients with severe illness or with neutropenia;
3. the current ambiguous SmPC statement risks inadvertently guiding physicians to depart from good clinical practice, including a potential to administer less appropriate antibacterial regimens than RECARBRIO, and is not consistent with SmPCs of other recently approved antibacterial agents;
4. the suggestion to use alternative therapies in otherwise imipenem/REL-susceptible pathogens is a departure from current antimicrobial stewardship principles and could lead to exposure to unnecessary combination regimens or higher doses of other antimicrobials which could potentially lead to toxicities;
5. new favourable clinical efficacy and safety data obtained from HAP/VAP patients (P014) with severe illness and risk factors for poor clinical outcomes demonstrated that the 500/500/250 mg dose of IMI/REL was efficacious, well tolerated and demonstrated adequate PTA achievement.
6. efficacy data from subgroups of the study population in the P014 study with most severe HAP/VAP infections.
7. In vitro susceptibility data to demonstrate the improved activity of IMI/RAL compared with IMI alone against IMI-susceptible aerobic Gram-negative organisms.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

P014

The P014 study included adult subjects fulfilling the criteria for HAP or VAP excluding those with a baseline LRT specimen Gram stain that showed the presence of Gram-positive cocci only. The inclusion and exclusion criteria were acceptable.

Subjects were randomised to receive IMI/REL 500/500/250 mg or PIP/TAZ 4000/500 mg q6h for 7 to 14 days. The IMI/REL doses studied were the same as recommended for the treatment of aerobic Gram-negative organisms in adults with limited treatment options. The choice and dose of the comparator was acceptable. The dose regimen was in line with that recommended for the treatment of nosocomial pneumonia in the EU SmPC (Art 30 referral EMEA/H/A-30/001149). Linezolid (600 mg q12h) was furthermore administered empirically for concomitant MRSA infection.

The primary endpoint was clinical response at the EFU visit 7 to 14 days after EOT. The MITT population was chosen as the primary analysis population. This is acceptable because the MITT population was essentially similar in numbers compared with the ITT population that will most likely be the recommended primary analysis population in the updated antibacterial guideline. The test of cure visit (in this specific case the EFU visit) should according to CHMP guidance occur at a minimum of number of days after completion of therapy but be defined in relation to randomisation and not EOT. There is however no reason to believe that the definition used influenced the primary analysis because of similar treatment durations in test and control groups.

Key secondary endpoint (primary for the US FDA) was all-cause mortality through day 28 in the MITT population.

The sample size was estimated to meet FDA requirements but also acceptable to the CHMP.

Randomisation was stratified based on ventilation status at randomisation (non-ventilated HAP versus ventilated HAP or VAP) and APACHE II score (<15 versus ≥15). In addition, randomisation was to be controlled such that at least 50% of randomised subjects were to be in the VAP or ventilated HAP stratum.

The methodologies for blinding and masking were acceptable.

There were separate statistical analysis plans for EU and the US FDA and the EU SAP was overall appropriate. There were no changes in the planned analyses following study unblinding and no post-hoc analyses performed.

A total of 583 participants were screened, 537 were randomised, and 535 received at least 1 dose of trial treatment (IMI/REL, 266 participants; PIP/TAZ, 269 participants). Approximately 70% completed the trial in both study groups. The main reason for discontinuation in both treatment groups were death with a higher number in the PIP/TAZ group. The second most common reason for discontinuation was that the subject moved, which was more common in the IMI/REL group [17/268 (6.3%) compared to 5/269 (1.9%) in the PIP/TAZ arm].

A higher number of subjects completed study medication in the IMI/REL group (~80%) compared to in the PIP/TAZ group (~70%). The imbalance was mainly driven by differences in number that discontinued study medication because of haemodialysis discontinuation criteria, physician's decision and treatment failure.

Demographic and baseline subject characteristics were generally comparable with regard to participant characteristics.

The overall mean APACHE II score was 14.7, with 47.5% of participants having an APACHE II score ≥15 and 23.4% of participants having an APACHEII score ≥20. Overall, 48.6% of participants had a primary diagnosis of ventilated HAP/VAP.

Aerobic gram-negative bacilli were predominant in both treatment groups, and the most frequently isolated was *K. pneumoniae*. *P. aeruginosa* was the next most common pathogen. The distribution of pathogens in both treatment groups was generally comparable, except for *P. aeruginosa*, which was isolated from a lower proportion of participants in the IMI/REL group.

Susceptibility to IMI/REL was generally high with >85% to 100% susceptibility to IMI/REL of key baseline pathogens isolated from the lower respiratory tract except *Acinetobacter* which had a very low susceptible rate (12.5%) using EUCAST BPs. This finding is discussed further below.

Lower susceptibility rates to PIP/TAZ compared with IMI/REL was generally noted against various Enterobacterales and *P. aeruginosa*. There are no EUCAST BPs set for PIP/TAZ against Acinetobacter but CLSI breakpoints (not shown) revealed very low susceptibility rates (13.5%).

The numbers of subjects with pathogens isolated from blood were low in both treatment groups.

Compliance and exposure to study drug and prior and concomitant exposure to other antibacterial agents were well balanced between the treatment groups. Notably, approximately 10% of participants received colistin or polymyxins which is of interest in the light of the high proportion of subjects with Acinetobacter isolated at baseline resistant to IMI/REL and PIP/TAZ. Very few randomised participants (six in total) were excluded from the MITT population as commented above.

Exclusions from other important analysis populations (mMITT and CE populations) were essentially similar across treatment groups.

Efficacy data and additional analyses

IMI/REL was non-inferior to PIP/TAZ in participants with HAP/VAP, as assessed by the incidence rate of favourable clinical response at the EFU visit in the MITT population (61.0% vs. 55.8%; adjusted difference 5.0%; 95% CI -3.2, 13.2). Among participants allocated to randomisation strata with baseline APACHE II ≥15, those treated with IMI/REL had a numerically higher favourable clinical response compared to PIP/TAZ, regardless of ventilation status.

IMI/REL was also non-inferior to PIP/TAZ in participants with HAP/VAP, as assessed by the incidence rate of all-cause mortality through Day 28 in the MITT population (15.9% vs. 21.3%; adjusted difference -5.3%; 95% CI -11.9, 1.2). Among participants allocated to either strata with APACHE II ≥15, those treated with IMI/REL had a numerically lower rate of all-cause mortality compared to those treated with PIP/TAZ, regardless of ventilation status.

The proportion of participants with favourable clinical response at the EFU visit in the CE population was essentially similar in the treatment groups (74.3% vs. 79.4%).

In the mMITT and ME populations, the proportion of participants achieving favourable overall microbiological response rates were also comparable across treatment groups at the EFU visit.

The proportion of subjects achieving favourable clinical response at EFU by baseline pathogen from LRT culture were essentially comparable across treatment groups for the most commonly isolated key Gram-negative pathogens (*Acinetobacter* spp., *E. coli*, *K. pneumoniae*) except for *P. aeruginosa* (~40% for IMI/REL vs. ~60% for PIP/TAZ). The proportion of subjects achieving favourable microbiological response at EFU by baseline pathogen from LRT culture were essentially comparable across treatment groups for the most commonly isolated key Gram-negative pathogens (including *P. aeruginosa*; ~50% for IMI/REL vs. ~60% for PIP/TAZ). The MAH has explained that the difference in clinical and microbiological favourable response for *P. aeruginosa* at EFU could be explained by that a higher number of subjects in the IMI/REL group infected with this pathogen developed non-disease related clinical events or died due to non-pneumonia aetiologies.

The rate of favourable clinical and microbiological response was unexpectedly similarly high for subjects with *Acinetobacter* (for which the susceptibility rates were very low) as those subjects with high susceptibility rates (e.g. *E. coli* and *K. pneumoniae*). It is important to note that the high favourable clinical response rates for subjects in both treatment groups, from whom *Acinetobacter* spp. were isolated from the lower respiratory tract, was not driven by the use of colistin/polymyxins because use of concomitant non-study antibacterial agents rendered the subject a failure in the analyses. There is no doubt that *Acinetobacter* spp. could cause HAP/VAP. However, whether Acinetobacter having high MICs isolated from subjects with a favourable outcome actually caused the infection could be questioned because favourable outcome would not be expected. This has implications for the list of pathogens in the SmPC proposed by the MAH against which Recarbrio has been shown to have demonstrated clinical effect. Notably, only 4 out of 32 isolates were considered susceptible to IMI/REL using EUCAST susceptibility interpretive criteria.

Essentially similar incidence rates for favourable clinical response at the EFU visit and all-cause mortality through Day 28 were observed for both treatment groups across subgroups, consistent with the results of the primary and key secondary efficacy analyses.

Efficacy data to support the claimed indications

The P014 study was designed to support the claimed indications treatment of HAP including VAP, with or without concurrent bacteraemia in adults, indications already approved for IMI alone. Therefore, the main issue is that the recommended doses of REL are sufficient in these conditions to protect IMI from hydrolysis

of relevant beta-lactamases. It was not expected, nor requested, that the HAP/VAP study should enrol sufficient organisms that were resistant to IMI but susceptible to IMI/REL to demonstrate a clinical benefit of adding REL and/or substantiate the adequacy of the REL dose regimen. Therefore, the PTA analyses to support the dose regimens (and thus the PK data obtained from the P014 study) and data to demonstrate that REL adequately penetrates to the lung, i.e. epithelial lining fluid (ELF), are of paramount importance. The penetration to ELF was assessed in the initial approval of Recarbrio. The PTA is assessed in the clinical pharmacology section.

The MAH´s proposal for section 4.4 of the SmPC

The MAH proposes to delete the following paragraph from section 4.4 of the SmPC:

> *Neutropenic patients and patients with very severe infections*
>
> *The recommended doses of Recarbrio may not be optimal to treat i) patients with neutropenia or ii) patients with very severe infections. Consideration should be given to using alternative therapies for these patients.*

Despite that nothing is known of the clinical effects using the highest approved and recommended dose of IMI alone (1 g q6h) in combination with an adequate amount of REL in the FDC there are obviously data from relevant subgroups in the P014 study (patients with HAP/VAP treated in the ICU at baseline, patients with APACHE score ≥15 at baseline, patients with moderate or severe renal impairment at baseline and patients receiving vasopressors) in support of treatment of infections that could be considered "very severe" at the 500/250 mg q6h dose of IMI/REL compared with a relevant comparator at its highest recommended dose. There were furthermore no concerns with regards to efficacy in the subgroups of ventilated HAP/VAP and subjects with higher CPIS scores which lends further support that the dose of IMI/REL is acceptable for those subjects with most severe infections. Without concerns based on the subgroup analysis from the P014 study, the paragraph could be considered redundant and misleading.

The warning statement was introduced at initial approval based on precedent wording in the harmonised Tienam EU SmPC. However, from a regulatory perspective it is reasonable to also take into account what is stated in the SmPC for the comparator used in the HAP/VAP study. There is no warning statement for the treatment of "very severe" infections in the PIP/TAZ SmPC which has been harmonised during an Article 30 referral (EMEA/H/A-30/1149). HAP/VAP is one of the infection types that considered most "severe". Without concerns for efficacy of IMI/REL in relevant subgroups within the HAP/VAP population that could be considered "very severe" as discussed above, it is considered reasonable to remove the warning statement with regards "very severe infections".

Moreover, in vitro activity data for IMI alone and IMI/REL in combination demonstrates that modal MICs are lower with the combination for several aerobic gram-negative organisms within the subset of susceptible organisms because many of these are expressing betalactamases within the spectrum of RELs inhibitory activity. Consequently, the MIC of an isolate may be lower for IMI/REL than for IMI alone, although the pathogen is susceptible to both, which means that the pharmacodynamic activity will be improved for IMI/REL at similar IMI dosages. For isolates considered wild-type (without acquired resistance mechanisms), against which REL is not expected to contribute to the activity of IMI alone, MICs are in general several dilution steps lower than the susceptibility breakpoint and therefore there is no concern with regards the 500/250 mg q6h IMI/REL dose with regards adequate pharmacodynamic activity. The epidemiological cut-off (ECOFF), which is the MIC at the upper end of the wild-type population, is moreover one or more dilution steps below the susceptibility breakpoint for many relevant Gram-negative organisms for both IMI and IMI/REL. For *P. aeruginosa* the epidemiological cut-off (ECOFF) is unexpectedly lower for the combination (1 mg/L for IMI/REL compared with 4 mg/L for IMI alone). These in vitro activity data demonstrates the often more pronounced effect of the combination and lends furthermore support that it

may not be relevant to extrapolate conclusions drawn for IMI alone with regards the 500 mg q6h compared with 1000 mg q6h dose for IMI combined with REL.

With regards neutropenia it should be noted that subjects with immunosuppression, including those with neutropenia, were excluded from the P014 study. The Company considers this to be a limitation of clinical data rather than inferring any caution regarding the dose recommendation for this group of patients and proposes to delete the whole paragraph and replace be introducing a limitation of clinical data statement. This would be in line with how limitations have been handled for other recently approved antibacterial agents and is thus considered acceptable.

In summary, there are relevant data and acceptable arguments for the removal of the warning statement and amendment of the SmPC with regards patients with neutropenia which were excluded from the clinical studies.

2.4.3. Conclusions on the clinical efficacy

In summary, the clinical benefit of adding REL to IMI for the treatment of the already approved indications for IMI now applied for IMI/REL was not expected to be demonstrated by the clinical efficacy data from the P014 study. The added value of REL is assessed in the clinical pharmacology section. Some issues for clarifications were identified but are not further pursued since the responses are not expected to have any impact on the acceptability of the indications applied for.

2.5. Clinical safety

Introduction

The safety data base to support this type II variation consist of the P014 study which is described in more detail in the Section for Clinical Efficacy. Adverse events that occurred during the IV treatment period and during the 14-day follow-up period were reported. MedDRA version 22.0 was used to classify the AEs.

Patient exposure

Safety analyses were based on all randomized subjects that received at least one dose of trial treatment (ASaT) population, which included 535 randomized subjects (266 in the IMI/REL group; 269 in the PIP/TAZ group). The exposure as well as demographics are described in the Section for Clinical Efficacy.

Adverse events

Table 1. Adverse Event Summary During IV Therapy and 14-Day Follow-Up Period All Subjects as Treated Population IMI

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	266		269		535	
with one or more adverse events	226	(85.0)	233	(86.6)	459	(85.8)
with no adverse event	40	(15.0)	36	(13.4)	76	(14.2)
with drug-related[†] adverse events	31	(11.7)	26	(9.7)	57	(10.7)
with serious adverse events	71	(26.7)	86	(32.0)	157	(29.3)
with serious drug-related adverse events	3	(1.1)	2	(0.7)	5	(0.9)
who died	40	(15.0)	57	(21.2)	97	(18.1)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	15	(5.6)	22	(8.2)	37	(6.9)
discontinued drug due to a drug-related adverse event	6	(2.3)	4	(1.5)	10	(1.9)
discontinued drug due to a serious adverse event	9	(3.4)	18	(6.7)	27	(5.0)
discontinued drug due to a serious drug-related adverse event	2	(0.8)	1	(0.4)	3	(0.6)

[†] Determined by the investigator to be related to the drug.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

Table 2. Subjects with Specific Adverse Events During IV Therapy and 14-Day Follow-Up Period (Incidence ≥ 5% in One or More Treatment Groups) All Subjects as Treated Population

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	266		269		535	
with one or more adverse events	226	(85.0)	233	(86.6)	459	(85.8)
with no adverse events	40	(15.0)	36	(13.4)	76	(14.2)
Blood and lymphatic system disorders	**45**	**(16.9)**	**49**	**(18.2)**	**94**	**(17.6)**
Anaemia	28	(10.5)	27	(10.0)	55	(10.3)
Cardiac disorders	**41**	**(15.4)**	**32**	**(11.9)**	**73**	**(13.6)**
Gastrointestinal disorders	**60**	**(22.6)**	**70**	**(26.0)**	**130**	**(24.3)**
Diarrhoea	21	(7.9)	30	(11.2)	51	(9.5)
General disorders and administration site conditions	**32**	**(12.0)**	**51**	**(19.0)**	**83**	**(15.5)**
Pyrexia	11	(4.1)	20	(7.4)	31	(5.8)
Infections and infestations	**83**	**(31.2)**	**77**	**(28.6)**	**160**	**(29.9)**
Injury, poisoning and procedural complications	**14**	**(5.3)**	**21**	**(7.8)**	**35**	**(6.5)**
Investigations	**63**	**(23.7)**	**51**	**(19.0)**	**114**	**(21.3)**
Alanine aminotransferase increased	26	(9.8)	19	(7.1)	45	(8.4)
Aspartate aminotransferase increased	31	(11.7)	20	(7.4)	51	(9.5)
Metabolism and nutrition disorders	**59**	**(22.2)**	**56**	**(20.8)**	**115**	**(21.5)**
Hypokalaemia	18	(6.8)	24	(8.9)	42	(7.9)
Hyponatraemia	14	(5.3)	3	(1.1)	17	(3.2)
Nervous system disorders	**28**	**(10.5)**	**34**	**(12.6)**	**62**	**(11.6)**
Psychiatric disorders	**14**	**(5.3)**	**20**	**(7.4)**	**34**	**(6.4)**
Renal and urinary disorders	**23**	**(8.6)**	**30**	**(11.2)**	**53**	**(9.9)**
Respiratory, thoracic and mediastinal disorders	**67**	**(25.2)**	**59**	**(21.9)**	**126**	**(23.6)**
Hydrothorax	11	(4.1)	14	(5.2)	25	(4.7)
Skin and subcutaneous tissue disorders	**35**	**(13.2)**	**27**	**(10.0)**	**62**	**(11.6)**
Vascular disorders	**29**	**(10.9)**	**29**	**(10.8)**	**58**	**(10.8)**

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

The majority of the reported AEs were mild-moderate at intensity. The most commonly reported severe AEs (≥5 subject in at least one of the treatment groups) were cardiac arrest (10 [3.8%] for IMI/REL and 8[3%] for PIP/TAZ), anaemia (8 [3%] for IMI/REL and 6 [2.2%] for PIP/TAZ), septic shock (7 [2.6%] for IMI/REL and 2 [0.7%] for PIP/TAZ), multiple organ dysfunction syndrome (1 [0.4%] for IMI/REL and 7 [2.6%] for PIP/TAZ), and pneumonia (6 [2.3%] for IMI/REL and 3 [1.1%] for PIP/TAZ).

Drug related AEs

Table 3. Subjects with Drug-Related Adverse Events During IV Therapy and 14-Day Follow-Up Period (Incidence > 0% in One or More Treatment Groups) All Subjects as Treated Population

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	266		269		535	
with one or more adverse events	31	(11.7)	26	(9.7)	57	(10.7)
with no adverse events	235	(88.3)	243	(90.3)	478	(89.3)
Blood and lymphatic system disorders	**4**	**(1.5)**	**1**	**(0.4)**	**5**	**(0.9)**
Leukopenia	0	(0.0)	1	(0.4)	1	(0.2)
Thrombocytopenia	4	(1.5)	0	(0.0)	4	(0.7)
Gastrointestinal disorders	**9**	**(3.4)**	**9**	**(3.3)**	**18**	**(3.4)**
Diarrhoea	6	(2.3)	6	(2.2)	12	(2.2)
Dysbiosis	0	(0.0)	1	(0.4)	1	(0.2)
Epigastric discomfort	0	(0.0)	1	(0.4)	1	(0.2)
Faeces soft	1	(0.4)	0	(0.0)	1	(0.2)
Nausea	1	(0.4)	1	(0.4)	2	(0.4)
Vomiting	2	(0.8)	1	(0.4)	3	(0.6)
General disorders and administration site conditions	**3**	**(1.1)**	**4**	**(1.5)**	**7**	**(1.3)**
Infusion site pain	0	(0.0)	1	(0.4)	1	(0.2)
Injection site pain	0	(0.0)	1	(0.4)	1	(0.2)
Injection site phlebitis	1	(0.4)	0	(0.0)	1	(0.2)
Injection site reaction	0	(0.0)	1	(0.4)	1	(0.2)
Injection site swelling	2	(0.8)	1	(0.4)	3	(0.6)
Pyrexia	0	(0.0)	1	(0.4)	1	(0.2)
Hepatobiliary disorders	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.2)**
Hepatic function abnormal	1	(0.4)	0	(0.0)	1	(0.2)
Infections and infestations	**4**	**(1.5)**	**2**	**(0.7)**	**6**	**(1.1)**
Antibiotic associated colitis	1	(0.4)	0	(0.0)	1	(0.2)
Clostridium difficile colitis	1	(0.4)	0	(0.0)	1	(0.2)
Fungal disease carrier	0	(0.0)	1	(0.4)	1	(0.2)
Fungal skin infection	0	(0.0)	1	(0.4)	1	(0.2)
Gastroenteritis	1	(0.4)	0	(0.0)	1	(0.2)
Vulvovaginal candidiasis	1	(0.4)	0	(0.0)	1	(0.2)

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**1**	**(0.4)**	**1**	**(0.2)**
Infusion related reaction	0	(0.0)	1	(0.4)	1	(0.2)
Investigations	**10**	**(3.8)**	**4**	**(1.5)**	**14**	**(2.6)**
Alanine aminotransferase increased	6	(2.3)	3	(1.1)	9	(1.7)
Aspartate aminotransferase increased	6	(2.3)	0	(0.0)	6	(1.1)
Blood alkaline phosphatase increased	4	(1.5)	1	(0.4)	5	(0.9)
Blood potassium decreased	1	(0.4)	0	(0.0)	1	(0.2)
Blood sodium increased	1	(0.4)	0	(0.0)	1	(0.2)
Gamma-glutamyltransferase increased	1	(0.4)	1	(0.4)	2	(0.4)
Platelet count decreased	1	(0.4)	0	(0.0)	1	(0.2)
Metabolism and nutrition disorders	**2**	**(0.8)**	**1**	**(0.4)**	**3**	**(0.6)**
Hypokalaemia	2	(0.8)	1	(0.4)	3	(0.6)
Hypomagnesaemia	1	(0.4)	0	(0.0)	1	(0.2)
Hyponatraemia	1	(0.4)	0	(0.0)	1	(0.2)
Nervous system disorders	**0**	**(0.0)**	**2**	**(0.7)**	**2**	**(0.4)**
Dizziness	0	(0.0)	1	(0.4)	1	(0.2)
Dysgeusia	0	(0.0)	1	(0.4)	1	(0.2)
Generalised tonic-clonic seizure	0	(0.0)	1	(0.4)	1	(0.2)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.4)**	**1**	**(0.2)**
Hallucination, visual	0	(0.0)	1	(0.4)	1	(0.2)
Renal and urinary disorders	**0**	**(0.0)**	**1**	**(0.4)**	**1**	**(0.2)**
Renal impairment	0	(0.0)	1	(0.4)	1	(0.2)
Skin and subcutaneous tissue disorders	**6**	**(2.3)**	**2**	**(0.7)**	**8**	**(1.5)**
Petechiae	1	(0.4)	0	(0.0)	1	(0.2)
Pruritus generalised	0	(0.0)	1	(0.4)	1	(0.2)
Rash	3	(1.1)	1	(0.4)	4	(0.7)
Rash generalised	1	(0.4)	0	(0.0)	1	(0.2)
Skin and subcutaneous tissue disorders	**6**	**(2.3)**	**2**	**(0.7)**	**8**	**(1.5)**
Urticaria	1	(0.4)	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

Table 4. Adverse Event Summary by Pneumonia Type of Primary Diagnosis During IV Therapy and 14-Day Follow-Up Period All Subjects as Treated Population

	Non-Ventilated HABP				Ventilated HABP				VABP			
	IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	142		133		31		35		93		101	
with one or more adverse events	112	(78.9)	107	(80.5)	29	(93.5)	35	(100.0)	85	(91.4)	91	(90.1)
with no adverse event	30	(21.1)	26	(19.5)	2	(6.5)	0	(0.0)	8	(8.6)	10	(9.9)
with drug-related[T] adverse events	22	(15.5)	13	(9.8)	2	(6.5)	4	(11.4)	7	(7.5)	9	(8.9)
with serious adverse events	30	(21.1)	25	(18.8)	14	(45.2)	21	(60.0)	27	(29.0)	40	(39.6)
with serious drug-related adverse events	0	(0.0)	1	(0.8)	1	(3.2)	0	(0.0)	2	(2.2)	1	(1.0)
who died	17	(12.0)	18	(13.5)	8	(25.8)	15	(42.9)	15	(16.1)	24	(23.8)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	5	(3.5)	8	(6.0)	3	(9.7)	6	(17.1)	7	(7.5)	8	(7.9)
discontinued drug due to a drug-related adverse event	3	(2.1)	3	(2.3)	1	(3.2)	0	(0.0)	2	(2.2)	1	(1.0)
discontinued drug due to a serious adverse event	1	(0.7)	6	(4.5)	3	(9.7)	5	(14.3)	5	(5.4)	7	(6.9)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	1	(0.8)	1	(3.2)	0	(0.0)	1	(1.1)	0	(0.0)

[T] Determined by the investigator to be related to the drug.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

Serious adverse events / deaths / other significant events

Among the subjects treated with IMI/REL, 71 (26.7%) were reported with SAEs during the treatment period or the 14-day follow up period, for the subjects treated with PIP/TAZ the corresponding number was 86 (32%). Of the serious AEs were five classified as drug-related by the investigator (3 in the IMI/REL group and 2 in the PIP/TAZ group).

The most commonly reported SAEs (≥5 subject in at least one of the treatment groups) were septic shock (7 [2.6%] for IMI/REL and 4 [1.5%] for PIP/TAZ), cardiac arrest (10 [3.8%] for IMI/REL and 7 [2.6%] for PIP/TAZ) and pneumonia (6 [2.3%] for IMI/REL and 3 [1.1%] for PIP/TAZ).

Death

During the treatment period or the 14-day follow up period 40 (15%) subjects treated with IMI/REL and 57 (21.2%) of the subjects treated with PIP/TAZ died. None of deaths were considered drug related by the investigator.

The most common AEs that led to death (≥5 subject in at least one of the treatment groups) were cardiac arrest (9 [3.4%] for IMI/REL and 6 [2.2%] for PIP/TAZ), septic shock (6 [2.3%] for IMI/REL and 2 [0.7%] for PIP/TAZ), and multiple organ dysfunction syndrome (1 [0.4%] for IMI/REL and 6 [2.2%] for PIP/TAZ).

Laboratory findings

Vital signs

Mean change from baseline were generally comparable between the two treatment groups in terms of blood pressure, heart rate, respiratory rate and body temperature.

Haematology

Mean change from baseline were generally comparable between the two treatment groups.

Table 5. Hematology During IV Therapy and 14-Day Follow-Up Period All Subjects as Treated Population

	IMI/REL(N=266)					PIP/TAZ(N=269)					
	Maximum Grade during Post-baseline Period					Maximum Grade during Post-baseline Period					Difference vs. PIP/TAZ
Baseline Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	% (95% CI)[†]
Hemoglobin (g/dL)											
Grade 0: >10.5	53 (24.4)	22 (10.1)	17 (7.8)	3 (1.4)	1 (0.5)	72 (31.3)	18 (7.8)	17 (7.4)	2 (0.9)	0 (0.0)	
Grade 1: ≥9.5 to ≤10.5	7 (3.2)	18 (8.3)	24 (11.1)	7 (3.2)	0 (0.0)	1 (0.4)	18 (7.8)	22 (9.6)	6 (2.6)	1 (0.4)	
Grade 2: ≥8.0 to <9.5	2 (0.9)	7 (3.2)	26 (12.0)	12 (5.5)	2 (0.9)	1 (0.4)	4 (1.7)	20 (8.7)	25 (10.9)	0 (0.0)	
Grade 3: ≥6.5 to <8.0	0 (0.0)	0 (0.0)	4 (1.8)	9 (4.1)	2 (0.9)	0 (0.0)	2 (0.9)	4 (1.7)	14 (6.1)	2 (0.9)	
Grade 4: <6.5	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	
Elevation to Grade 3 or 4			n/m (%) 27/217 (12.4)					n/m (%) 36/230 (15.7)			-3.2 (-9.7, 3.3)
Platelets (10^9/L)											
Grade 0: ≥100	186 (91.2)	6 (2.9)	2 (1.0)	2 (1.0)	0 (0.0)	202 (93.1)	4 (1.8)	3 (1.4)	1 (0.5)	1 (0.5)	
Grade 1: ≥75 to <100	2 (1.0)	2 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	4 (1.8)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	
Grade 2: ≥50 to <75	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	
Grade 3: ≥20 to <50	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 4: <20	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Elevation to Grade 3 or 4			n/m (%) 3/204 (1.5)					n/m (%) 3/217 (1.4)			0.1
Leukocytes (10^9/L)											
Grade 0: ≥1 to <11	57 (26.8)	18 (8.5)	18 (8.5)	17 (8.0)	0 (0.0)	54 (24.0)	13 (5.8)	10 (4.4)	19 (8.4)	1 (0.4)	
Grade 1: ≥11 to <13	13 (6.1)	7 (3.3)	3 (1.4)	11 (5.2)	0 (0.0)	10 (4.4)	7 (3.1)	5 (2.2)	11 (4.9)	0 (0.0)	
Grade 2: ≥13 to <15	10 (4.7)	4 (1.9)	4 (1.9)	7 (3.3)	1 (0.5)	10 (4.4)	1 (0.4)	3 (1.3)	10 (4.4)	1 (0.4)	
Grade 3: ≥15 to ≤30	3 (1.4)	5 (2.3)	5 (2.3)	22 (10.3)	3 (1.4)	4 (1.8)	14 (6.2)	6 (2.7)	37 (16.4)	5 (2.2)	
Grade 4: >30 or <1	0 (0.0)	0 (0.0)	1 (0.5)	3 (1.4)	1 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.9)	1 (0.4)	
Elevation to Grade 3 or 4			n/m (%) 39/213 (18.3)					n/m (%) 47/225 (20.9)			-2.6 (-10.0, 4.9)

[†] 95% confidence intervals are based on Miettinen & Nurminen method, and presented if n ≥ 4 in one of the treatment group.
n/m = number of subjects with elevation to Grade 3 or 4 / number of subjects with baseline and post-baseline assessments.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adlb]

Renal function

During the trial, the central safety laboratory experienced an equipment malfunction between OCT 2016 and JAN 2017. The equipment malfunction resulted in sporadic reporting of falsely higher serum creatinine concentrations. No other chemistry or haematological parameters were affected. Forty potentially erroneous creatinine values were recorded for 12 participants (6 in the IMI/REL group; 6 in the PIP/TAZ group). Initial dosing and adjustments of trial treatment based on renal function were calculated using local laboratory values, this error had no impact on dosing regimen. Those subjects are included in the table below.

Table 6. Creatinine Results During IV Therapy and 14-Day Follow-Up Period All Subjects as Treated Population

	IMI/REL(N=266)					PIP/TAZ(N=269)					
	Maximum Grade during Post-baseline Period					Maximum Grade during Post-baseline Period					Difference vs. PIP/TAZ
Baseline Grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	% (95% CI)[†]
Creatinine (mg/dL) [‡]											
Grade 0: <1.1 x ULN	212 (86.9)	7 (2.9)	4 (1.6)	0 (0.0)	0 (0.0)	203 (81.5)	12 (4.8)	9 (3.6)	2 (0.8)	0 (0.0)	
Grade 1: ≥1.1 to ≤1.5 x ULN	8 (3.3)	4 (1.6)	1 (0.4)	1 (0.4)	0 (0.0)	3 (1.2)	5 (2.0)	5 (2.0)	1 (0.4)	0 (0.0)	
Grade 2: >1.5 to ≤3.0 x ULN	1 (0.4)	2 (0.8)	2 (0.8)	2 (0.8)	0 (0.0)	1 (0.4)	2 (0.8)	4 (1.6)	2 (0.8)	0 (0.0)	
Grade 3: >3.0 to ≤6.0 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 4: >6.0 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Elevation to Grade 3 or 4			n/m (%) 3/244 (1.2)					n/m (%) 5/249 (2.0)			-0.8 (-3.5, 1.8)

[†] 95% confidence intervals are based on Miettinen & Nurminen method, and presented if n ≥ 4 in one of the treatment group.
[‡] Due to an equipment malfunction 40 potentially erroneous values were recorded for 12 subjects (6 subjects in IMI/REL group and 6 subjects in PIP/TAZ group); the potentially erroneous values were included in this analysis.
n/m = number of subjects with elevation to Grade 3 or 4 / number of subjects with baseline and post-baseline assessments.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adlb]

Liver function tests

During the IV therapy and the 14-day follow up period, the subjects described in the table below met the ECI criteria of post-baseline elevated liver transaminases.

Table 7. Subjects with Hepatic Transaminase Events of Clinical Interest During IV Therapy and 14-Day Follow-Up Period

	IMI/REL		PIP/TAZ		Difference in % vs. PIP/TAZ		
	n	(%)	n	(%)	Estimate	(95% CI)[†]	P Value[†]
Subjects in population	266		269				
Number of subjects with post-baseline elevated AST or ALT ≥ 3 X ULN and elevated Total Bilirubin ≥ 2 X ULN and Alkaline Phosphatase < 2 X ULN	1	(0.4)	3	(1.1)	-0.7	(-2.9, 1.1)	0.321
Number of subjects with confirmed AST or ALT ≥ 5 X ULN	6	(2.3)	4	(1.5)	0.8	(-1.8, 3.5)	0.512

[†] Based on Miettinen and Nurminen method.
ALT = alanine transaminase; AST = aspartate aminotransferase; ULN = upper limit of normal
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; addili]

One subject treated with IMI/REL met the criteria for Hy´s law. The subject had a history of hospitalization with multiple traumatic injury, cholelithiasis, acute kidney injury and atelectasis. Nineteen days following the hospitalization, the subject was diagnosed with VAP and treatment with IMI/REL was initiated (Day 1). On Day 2 the subject had pneumothorax and mild abnormal hepatic function. On Day 3 the subject discontinued study medication due to the physician's decision and entered Follow-up. The physician's decision was partly based on the respiratory samples results showing *Klebsiella pneumoniae* resistant to piperacillin (+) tazobactam and *Staphylococcus aureus*. There was no apparent clinical response to the study treatment by Day 3. The subject was diagnosed with pneumonia (severe) and was treated with cloxacillin and meropenem. Local laboratory results showed elevations of liver transaminase levels satisfying the laboratory parameters defined for clinical interest: increased AST levels ≥3 × ULN (199 IU/L), increased ALP levels ≥2 × ULN (313 IU/L [baseline: 192 IU/L, NR: 43-115 IU/L]), and bilirubin levels ≥2 × ULN (4.7 mg/dL). The PI's assessment of the reported impaired liver function at baseline and worsening of these laboratory results was caused by the subject's medical history of hepatic steatosis. Jaundice of the skin and mucous membranes was also observed. The subject's condition worsened with hypotension and increased ventilatory effort with an increase in RR (27 breaths/min). The subject was treated with fluids, increased ventilatory support and vasoactive amines due to refractory hypotension. On Day 4 hypotension worsened (BP: 57/34 mm Hg) and HR decreased (55 beats/min). There was no clinical response to antibiotic treatment and the subject had a cardiorespiratory arrest, which did not respond to treatment. The subject died and the cause of death was bacterial infection (polymicrobial infection). No autopsy was performed.

Safety in special populations

Age

Table 8. Subjects Who Received IMI/REL with Selected Adverse Events by Age Group (Incidence > 0% in Any Column) During IV Therapy and 14-Day Follow-Up in Study P014 All Subjects as Treated (N = 266)

MedDRA Term	Age < 65 (N=153) n (%)	Age 65 - 74 (N=58) n (%)	Age 75 - 84 (N=39) n (%)	Age 85+ (N=16) n (%)
Total AEs	126 (82.4)	49 (84.5)	36 (92.3)	15 (93.8)
Serious AEs	31 (20.3)	18 (31.0)	19 (48.7)	3 (18.8)
Fatal	13 (8.5)	14 (24.1)	11 (28.2)	2 (12.5)
Hospitalization/prolong existing hospitalization	20 (13.1)	5 (8.6)	11 (28.2)	1 (6.3)
Life-threatening	18 (11.8)	9 (15.5)	11 (28.2)	1 (6.3)
Disability/incapacity	0 (0.0)	1 (1.7)	1 (2.6)	0 (0.0)
Other (medically significant)	4 (2.6)	0 (0.0)	2 (5.1)	0 (0.0)
AE leading to drop-out	7 (4.6)	2 (3.4)	4 (10.3)	2 (12.5)
Psychiatric disorders	8 (5.2)	1 (1.7)	4 (10.3)	1 (6.3)
Nervous system disorders	17 (11.1)	6 (10.3)	5 (12.8)	0 (0.0)
Accidents and injuries	5 (3.3)	0 (0.0)	1 (2.6)	1 (6.3)
Cardiac disorders	16 (10.5)	13 (22.4)	8 (20.5)	4 (25.0)
Vascular disorders	12 (7.8)	9 (15.5)	7 (17.9)	1 (6.3)
Cerebrovascular disorders	8 (5.2)	3 (5.2)	1 (2.6)	0 (0.0)
Infections and infestations	43 (28.1)	16 (27.6)	18 (46.2)	6 (37.5)
Anticholinergic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	2 (1.3)	0 (0.0)	2 (5.1)	0 (0.0)

N=number of ASAT IMI/REL subjects in Age categories. n= number of subjects with the adverse event.
Total row calculated subjects with at least one AE for all terms, other row calculated subjects with selected AE terms.

Gender

Table 9. Adverse Event Summary by Gender During IV Therapy and 14-Day Follow-Up Period All Subjects as Treated Population

	Male				Female			
	IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	180		191		86		78	
with one or more adverse events	150	(83.3)	165	(86.4)	76	(88.4)	68	(87.2)
with no adverse event	30	(16.7)	26	(13.6)	10	(11.6)	10	(12.8)
with drug-related† adverse events	21	(11.7)	16	(8.4)	10	(11.6)	10	(12.8)
with serious adverse events	49	(27.2)	62	(32.5)	22	(25.6)	24	(30.8)
with serious drug-related adverse events	2	(1.1)	1	(0.5)	1	(1.2)	1	(1.3)
who died	29	(16.1)	43	(22.5)	11	(12.8)	14	(17.9)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	10	(5.6)	12	(6.3)	5	(5.8)	10	(12.8)
discontinued drug due to a drug-related adverse event	3	(1.7)	1	(0.5)	3	(3.5)	3	(3.8)
discontinued drug due to a serious adverse event	7	(3.9)	10	(5.2)	2	(2.3)	8	(10.3)
discontinued drug due to a serious drug-related adverse event	1	(0.6)	0	(0.0)	1	(1.2)	1	(1.3)

† Determined by the investigator to be related to the drug.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

Race and ethnicity

Table 10. Adverse Event Summary by Race During IV Therapy and 14-Day Follow-Up Period All Subjects as Treated Population

	White				Non-White			
	IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	208		209		58		59	
with one or more adverse events	177	(85.1)	176	(84.2)	49	(84.5)	56	(94.9)
with no adverse event	31	(14.9)	33	(15.8)	9	(15.5)	3	(5.1)
with drug-related[†] adverse events	16	(7.7)	15	(7.2)	15	(25.9)	11	(18.6)
with serious adverse events	51	(24.5)	62	(29.7)	20	(34.5)	24	(40.7)
with serious drug-related adverse events	2	(1.0)	2	(1.0)	1	(1.7)	0	(0.0)
who died	29	(13.9)	42	(20.1)	11	(19.0)	15	(25.4)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	7	(3.4)	17	(8.1)	8	(13.8)	5	(8.5)
discontinued drug due to a drug-related adverse event	1	(0.5)	3	(1.4)	5	(8.6)	1	(1.7)
discontinued drug due to a serious adverse event	6	(2.9)	14	(6.7)	3	(5.2)	4	(6.8)
discontinued drug due to a serious drug-related adverse event	1	(0.5)	1	(0.5)	1	(1.7)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

Table 11. Adverse Event Summary by Ethnicity During IV Therapy and 14-Day Follow-Up Period All Subjects as Treated Population

	Hispanic or Latino				Not Hispanic or Latino				Not Reported				Unknown			
	IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	56		55		207		205		2		5		1		4	
with one or more adverse events	47	(83.9)	45	(81.8)	176	(85.0)	179	(87.3)	2	(100.0)	5	(100.0)	1	(100.0)	4	(100.0)
with no adverse event	9	(16.1)	10	(18.2)	31	(15.0)	26	(12.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related[†] adverse events	6	(10.7)	9	(16.4)	25	(12.1)	17	(8.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	19	(33.9)	22	(40.0)	51	(24.6)	60	(29.3)	1	(50.0)	1	(20.0)	0	(0.0)	3	(75.0)
with serious drug-related adverse events	0	(0.0)	2	(3.6)	3	(1.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	11	(19.6)	9	(16.4)	28	(13.5)	45	(22.0)	1	(50.0)	1	(20.0)	0	(0.0)	2	(50.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	4	(7.1)	7	(12.7)	10	(4.8)	14	(6.8)	1	(50.0)	1	(20.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	2	(3.6)	6	(2.9)	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	3	(5.4)	6	(10.9)	5	(2.4)	11	(5.4)	1	(50.0)	1	(20.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	1	(1.8)	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

Renal function

Table 12. Adverse Event Summary by Baseline Renal Function During IV Therapy and 14-Day Follow-Up Period All Subjects as Treated Population

	Normal				Mild				Moderate				Severe			
	IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ		IMI/REL		PIP/TAZ	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	142		136		53		72		61		48		10		13	
with one or more adverse events	119	(83.8)	119	(87.5)	42	(79.2)	60	(83.3)	55	(90.2)	42	(87.5)	10	(100.0)	12	(92.3)
with no adverse event	23	(16.2)	17	(12.5)	11	(20.8)	12	(16.7)	6	(9.8)	6	(12.5)	0	(0.0)	1	(7.7)
with drug-related[†] adverse events	11	(7.7)	11	(8.1)	6	(11.3)	6	(8.3)	10	(16.4)	6	(12.5)	4	(40.0)	3	(23.1)
with serious adverse events	22	(15.5)	36	(26.5)	13	(24.5)	25	(34.7)	33	(54.1)	19	(39.6)	3	(30.0)	6	(46.2)
with serious drug-related adverse events	1	(0.7)	1	(0.7)	0	(0.0)	0	(0.0)	2	(3.3)	0	(0.0)	0	(0.0)	1	(7.7)
who died	9	(6.3)	20	(14.7)	8	(15.1)	18	(25.0)	21	(34.4)	16	(33.3)	2	(20.0)	3	(23.1)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	7	(4.9)	10	(7.4)	1	(1.9)	5	(6.9)	6	(9.8)	3	(6.3)	1	(10.0)	4	(30.8)
discontinued drug due to a drug-related adverse event	3	(2.1)	1	(0.7)	1	(1.9)	1	(1.4)	1	(1.6)	0	(0.0)	1	(10.0)	2	(15.4)
discontinued drug due to a serious adverse event	4	(2.8)	8	(5.9)	0	(0.0)	4	(5.6)	5	(8.2)	3	(6.3)	0	(0.0)	3	(23.1)
discontinued drug due to a serious drug-related adverse event	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	0	(0.0)	1	(7.7)

[†] Determined by the investigator to be related to the drug.
Renal Function: normal = baseline creatinine clearance ≥ 90 mL/min; mild = baseline creatinine clearance ≥ 60 to < 90 mL/min; moderate = baseline creatinine clearance ≥ 30 to < 60 mL/min; severe = baseline creatinine clearance ≥ 15 to < 30 mL/min.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

Safety related to drug-drug interactions and other interactions

No new data regarding interactions are included in this application.

Discontinuation due to adverse events

Discontinuation due to AEs were reported in 15 (5.6%) of the subjects treated with IMI/REL and in 22 (8.2%) of the subjects treated with PIP/TAZ. The most commonly reported AEs leading to discontinuation of trial treatment (≥2 subjects in either treatment group), were acute kidney injury (0 subjects treated with IMI/REL and 4 subjects treated with PIP/TAZ), cardiac arrest (2 vs. 0), and brain dislocation syndrome (also known as brain herniation; 0 vs. 2). The AEs are presented in table below.

Ten of the subjects that discontinued trial treatment due to AEs that was considered related to study drug; 6 from the IMI/REL group and 4 from the PIP/TAZ group. The drug-related AEs reported from subjects treated with IMI/REL were increased ALAT and ASAT, rash, abnormal hepatic function, thrombocytopenia, increased platelet count, generalised rash.

Table 13. Subjects with Adverse Events Leading to Discontinuation of IV Therapy (Incidence > 0% in One or More Treatment Groups) All Subjects as Treated Population

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	266		269		535	
with one or more adverse events	15	(5.6)	22	(8.2)	37	(6.9)
Blood and lymphatic system disorders	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.2)**
Thrombocytopenia	1	(0.4)	0	(0.0)	1	(0.2)
Cardiac disorders	**2**	**(0.8)**	**0**	**(0.0)**	**2**	**(0.4)**
Cardiac arrest	2	(0.8)	0	(0.0)	2	(0.4)
General disorders and administration site conditions	**0**	**(0.0)**	**1**	**(0.4)**	**1**	**(0.2)**
Pyrexia	0	(0.0)	1	(0.4)	1	(0.2)
Hepatobiliary disorders	**1**	**(0.4)**	**2**	**(0.7)**	**3**	**(0.6)**
Hepatic function abnormal	1	(0.4)	0	(0.0)	1	(0.2)
Hypertransaminasaemia	0	(0.0)	1	(0.4)	1	(0.2)
Ischaemic hepatitis	0	(0.0)	1	(0.4)	1	(0.2)
Infections and infestations	**4**	**(1.5)**	**5**	**(1.9)**	**9**	**(1.7)**
Brain abscess	0	(0.0)	1	(0.4)	1	(0.2)
Catheter site infection	1	(0.4)	0	(0.0)	1	(0.2)
Meningitis	1	(0.4)	0	(0.0)	1	(0.2)
Neurological infection	0	(0.0)	1	(0.4)	1	(0.2)
Pneumonia	0	(0.0)	1	(0.4)	1	(0.2)
Pneumonia acinetobacter	0	(0.0)	1	(0.4)	1	(0.2)
Sepsis	1	(0.4)	0	(0.0)	1	(0.2)
Septic shock	0	(0.0)	1	(0.4)	1	(0.2)
Tuberculosis	1	(0.4)	0	(0.0)	1	(0.2)
Investigations	**2**	**(0.8)**	**2**	**(0.7)**	**4**	**(0.7)**
Alanine aminotransferase increased	1	(0.4)	1	(0.4)	2	(0.4)
Aspartate aminotransferase increased	1	(0.4)	0	(0.0)	1	(0.2)
Creatinine renal clearance decreased	0	(0.0)	1	(0.4)	1	(0.2)
Platelet count decreased	1	(0.4)	0	(0.0)	1	(0.2)

	IMI/REL		PIP/TAZ		Total	
	n	(%)	n	(%)	n	(%)
Nervous system disorders	**0**	**(0.0)**	**4**	**(1.5)**	**4**	**(0.7)**
Brain dislocation syndrome	0	(0.0)	2	(0.7)	2	(0.4)
Generalised tonic-clonic seizure	0	(0.0)	1	(0.4)	1	(0.2)
Seizure	0	(0.0)	1	(0.4)	1	(0.2)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.4)**	**1**	**(0.2)**
Hallucination, visual	0	(0.0)	1	(0.4)	1	(0.2)
Renal and urinary disorders	**1**	**(0.4)**	**5**	**(1.9)**	**6**	**(1.1)**
Acute kidney injury	0	(0.0)	4	(1.5)	4	(0.7)
Renal failure	1	(0.4)	1	(0.4)	2	(0.4)
Respiratory, thoracic and mediastinal disorders	**2**	**(0.8)**	**2**	**(0.7)**	**4**	**(0.7)**
Acute respiratory distress syndrome	1	(0.4)	0	(0.0)	1	(0.2)
Haemothorax	0	(0.0)	1	(0.4)	1	(0.2)
Respiratory distress	0	(0.0)	1	(0.4)	1	(0.2)
Respiratory failure	1	(0.4)	0	(0.0)	1	(0.2)
Skin and subcutaneous tissue disorders	**2**	**(0.8)**	**0**	**(0.0)**	**2**	**(0.4)**
Rash	1	(0.4)	0	(0.0)	1	(0.2)
Rash generalised	1	(0.4)	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
IMI/REL = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

Source: [P014MK7655A: adam-adsl; adae]

Post marketing experience

The combination of imipenem/cilastatin/relebactam is not marketed in any country (per 10th Oct 2019). Relebactam is not marketed in any country either alone or with any other drug. There is extensive post marketing experience with imipenem/cilastatin with over 30 years of global marketed use of Primaxin® and Tienam®.

2.5.1. Discussion on clinical safety

The safety data to support this type II variation is based on one phase III trial (P014) including 537 hospitalized subjects with HAP/VAP that was randomized 1:1 to treatment with either IMI/REL or PIP/TAZ. This is considered a reasonable number of included subjects to evaluate the safety for this type II variation. In total, there were 266 subjects exposed at least one to the previously authorized dose of imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg that was administration IV every 6 hours over 30 minutes. Since the included subjects were hospitalized and the treatment was administered IV, compliance with the treatment regimen was high.

A majority of the included subjects (85% of those treated with IMI/REL and 86,6% of those treated with PIP/TAZ) experienced at least one AE, and almost one third of the subjects were reported with serious adverse events (26,7% of those treated with IMI/REL and 32% of those treated with PIP/TAZ). The high number of reported AEs and SAEs are not surprising taken into account this vulnerable population with comorbid diseases.

The most commonly reported AEs among subjects treated with IMI/REL were anemia (10.5%), diarrhoea (7.9%), increased levels of alanine aminotransferase (9.8%) and aspartate aminotransferase (11.7%). There was no clear difference between the two treatment groups in terms of reported AEs. Anemia is described as a very rare adverse drug reaction in the SmPC for imipenem/cilastatin, and the higher frequency of anemia reported in this study is probably not related to study drug but rather to the infectious process. It is therefore suggested to keep the frequency very rare for anemia in section 4.8.

No new AEs not already included in the SmPC have been observed.

The number of serious AEs were somewhat higher in the population >65 years and a fatal outcome of the serious AEs were more common in the older age groups.

Discontinuation due to AEs were reported in 15 of the subjects treated with IMI/REL, of which six of the events were considered related to study drug, all of them are already known AEs associated with IMI/REL. The number of discontinuations for the comparator group was 22.

About half (53%) of the included subject treated with IMI/REL had a normal renal function and 4% had severe impaired renal function at baseline. The frequency of serious AEs as well as events of death were higher among subjects with impaired renal function. The SmPC addresses the need for dose reduction secondary to impaired renal function.

Regarding vital signs and haematology, no significant difference in the presented data has been observed between the subjects treated with IMI/REL and those treated with PIP/TAZ.

The MAH presented a table including creatinine results for all included subjects in which a majority had grade 0 at baseline. Post-treatment, 3-5% of the subjects in both treatment groups had increased creatinine level to grade 1-2, and two subjects treated with PIP/TAZ were reported with grade 3. MAH noted that 40 potentially false higher creatinine values were recorded for 12 participants (6 in the IMI/REL group; 6 in the PIP/TAZ group) due to malfunction of equipment, but the error did not change the dose administered. It would be of interest to know which of the samples that were affected, this is however not relevant since it would not change the information that is already included in the SmPC regarding increased creatinine and dose recommendations in subjects with impaired renal function.

One event that met the criteria for Hy´s law was presented. That subject was suffering from comorbid diseases, one of them was impaired liver function, and died due to cardiorespiratory arrest after four days with intensive care. The subject was treated with IMI/REL for two days, concomitant with other medication such as cloxacillin and meropenem, which makes it difficult to draw any firm conclusion whether treatment with IMI/REL had an impact on the worsened liver status or if other concomitant treatments played a role in this event. The issue regarding increased liver transaminases and association with hepatic failure is already covered in the SmPC, where hepatic failure is included in section 4.8 as a rare ADR and increased alanine aminotransferase and aspartate aminotransferase are described as common. This is considered sufficient.

2.5.2. Conclusions on clinical safety

Within this phase III trial, including a reasonable number of subjects, no new safety concerns not already known for imipenem/relebactam has been observed in this phase III trial. No outstanding safety issues remain.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted version 1.1 with their application and was requested to submit an updated RMP (version 2.0) as a result of the assessment. The (main) proposed RMP changes were the following:

-Data lock point has been updated to 22-JUL-2019 to reflect database lock date of study P014.

-Part II: update regarding incidence of HAP/VAP, information on clinical patient exposure and exclusion criteria from study P014 has been included and statement regarding marketing approval has been updated.

There have been no changes to the list of safety concerns for imipenem/cilastatin/relebactam with this RMP update. There continues to be no important identified risks, important potential risks, or missing information for the product.

2.7. Overall conclusion on the RMP

The changes to the RMP are acceptable.

2.8. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are also made to the PI to bring it in line with the current QRD template version 10.1.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.8.1. User consultation

A justification for not performing a new user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Recarbrio (INN) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Recarbrio (imipenem/cilastatin/relebactam; IMI/REL) is authorised for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

The MAH proposes to extend the indication for Recarbrio to also be indicated for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in adults and treatment of patients with bacteraemia that occurs with, or is suspected to be associated with HAP or VAP.

3.1.2. Available therapies and unmet medical need

HAP and VAP are among the most common hospital-acquired infections. Globally, pneumonia is one of the most common nosocomial infection with reported incidence estimates of up to 1.6% of hospital admissions. Mortality in patients with HAP/VAP are reported to be at least 20%. Among commonly isolated pathogens in HAP/VAP are *Staphylococcus aureus* (methicillin susceptible or resistant), Enterobacterales and non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* spp.

Treatment of HAP and VAP is empiric. According to international guidelines, initial antibacterial regimens should be designed to be active against the most commonly isolated pathogens and take into account mortality risk factors and likelihood of infections caused by methicillin-resistant *S. aureus* and MDR Gram-negative pathogens.

Beta-lactam antibacterial agents are commonly used to manage infections including HAP/VAP. Increasing resistance to beta-lactams, including the carbapenems, has led to some organisms being effectively untreatable or treatable only by a few alternative agents. Despite a few antibacterial agents addressing carbapenem resistance in Gram-negative organisms have become available the past years there remains an unmet medical need for additional antibacterial agents.

3.1.3. Main clinical studies

P014 was a phase 3, randomised, double-blind, multicentre study of IMI/REL (n=268) compared with piperacillin/tazobactam (PIP/TAZ; n=269) in hospitalised adult subjects with HAP/VAP. There was no requirement in this study that the infections should be caused by carbapenem-resistant pathogens. Those with a baseline lower respiratory tract (LRT) specimen Gram stain that showed the presence of Gram-positive cocci only were excluded from the study.

3.2. Favourable effects

IMI/REL was non-inferior to PIP/TAZ in participants with HAP/VAP, as assessed by the incidence rate of favourable clinical response at the early follow-up (EFU) visit in the MITT population (61.0% vs. 55.8%; adjusted difference 5.0%; 95% CI -3.2, 13.2). Among participants allocated to randomisation strata with baseline APACHE II ≥15, those treated with IMI/REL had a numerically higher favourable clinical response compared to PIP/TAZ, regardless of ventilation status.

IMI/REL was also non-inferior to PIP/TAZ in participants with HAP/VAP, as assessed by the incidence rate of all-cause mortality through Day 28 in the MITT population (15.9% vs. 21.3%; adjusted difference -5.3%; 95% CI -11.9, 1.2). Among participants allocated to either strata with APACHE II ≥15, those treated with IMI/REL had a numerically lower rate of all-cause mortality compared to those treated with PIP/TAZ, regardless of ventilation status.

Based on plasma probability of target attainment (PTA) simulations using relevant pharmacokinetic/pharmacodynamic targets (PDTs), the doses of IMI and REL in different renal function categories are satisfactory (PTA >90%) for the treatment of HAP/VAP caused by pathogens having IMI/REL MICs up to 2 mg/L. This finding was further supported by additional PTA analyses by accounting for ELF penetration.

Treatment of HAP/VAP with associated bacteraemia is already granted for IMI when used alone. Therefore, there is no concern regarding the IMI doses to treat patients who have bacteraemia in association with HAP/VAP. REL pharmacokinetics were essentially similar for subjects with and without bacteraemia which supports the doses recommended for REL also for subjects with HAP/VAP and associated bacteraemia.

3.3. Uncertainties and limitations about favourable effects

Treatment of HAP and VAP with or without associated bacteraemia are approved indications for IMI without the addition of REL (e.g. in Tienam). It was not expected, nor requested, that the P014 study should enrol sufficient organisms that were resistant to IMI but susceptible to IMI/REL to demonstrate a clinical benefit of adding REL and/or substantiate the adequacy of the REL dose regimen. Therefore, the acceptance of the applied indications for Recarbrio is dependent on PK/PD considerations to demonstrate that the dose of REL is sufficient to protect IMI from hydrolysis of relevant beta-lactamases in HAP/VAP with or without associated bacteraemia. The PTA analyses to support the dose regimens and data to demonstrate that REL adequately penetrates to the lung are therefore of paramount importance.

3.4. Unfavourable effects

The study population to support this application included 266 HAP/VAP subjects that received at least one dose of 500 mg imipenem + 250 mg relebactam as FDC administered IV. The comparator group included 269 HAP/VAP subjects treated with 4000 mg piperacillin+ 500 mg tazobactam.

A majority of the included subjects (85%) treated with IMI/REL experienced at least one AE, and almost one third (26.7%) of the subjects were reported with serious adverse events. The most frequently reported unfavourable effect among subjects treated with IMI/REL were anemia (10.5%), diarrhoea (7.9%), increased levels of alanine aminotransferase (9.8%) and aspartate aminotransferase (11.7%). There was no clear difference between the two treatment groups in terms of reported AEs. Anemia is described as a very rare adverse drug reaction in the SmPC for imipenem/cilastatin, and the higher frequency of anemia reported in this study is probably not related to study drug but rather to the infectious process. It is therefore suggested to keep the frequency very rare for anemia in section 4.8.

No new ADR not already included in the SmPC section 4.8 has been observed within this phase III trial.

Discontinuation rate due to adverse events was low in all treatment groups and not considered a major concern for this treatment. Primary reasons for not completing study treatment among IMI/REL treated subjects were adverse events such as abnormal hepatic function, thrombocytopenia, increased platelet count, rash, generalized rash and increased liver transaminases (one subject each).

3.5. Uncertainties and limitations about unfavourable effects

The study includes HAP/VAP subjects, who tend to have extensive comorbid conditions and several concomitant treatments.

3.6. Effects Table

Effects Table for Recarbrio for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) in adults and treatment of patients with bacteraemia that occurs with, or is suspected to be associated with HAP or VAP.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Favourable clinical	Favourable clinical response defined as cure, i.e. all	n/N	IMI/REL 161/264	PIP/TAZ 149/267	Adjusted difference:	P014

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
l respo nse	pre-therapy signs and symptoms of the index infection have resolved (or returned to "pre-infection status") AND no additional antibiotic therapy is required for the index infection at EFU in the MITT population	(%)	(61.0)	(55.8)	5.0%; 95% CI -3.2, 13.2 Non-inferiority criterium met The study was not designed to demonstrate a clinical benefit of adding REL and/or substantiate the adequacy of the REL dose regimen.	
All-ca use morta lity throu gh Day 28	Incidence of death by any cause through day 28 in the MITT population	n/N (%)	IMI/REL 42/264 (15.9)	PIP/TAZ 57/267 (21.3)	Adjusted difference: -5.3%; 95% CI -11.9, 1.2 Non-inferiority criterium met	P014
Dose justifi cation	PTA against target pathogens based on PTA simulations using non-clinical PDTs and clinical PK data				The doses of IMI and REL in different renal function categories are satisfactory (PTA >90%) for the treatment of HAP/VAP caused by pathogens having IMI/REL MICs up to 2 mg/L	Clin pharm section
Unfavourable Effects						
Anemi a	Outcome in one phase III trial	n/N (%)	IMI/REL 28/266 (10.5)	PIP/TAZ 27/269 (10.0)		P014
Diarrh oea	Outcome in one phase III trial	n/N (%)	IMI/REL 21/266 (7.9)	PIP/TAZ 30/269 (11.2)		P014
Incre ased ALAT	Outcome in one phase III trial	n/N (%)	IMI/REL 26/266 (9.8)	PIP/TAZ 19/269 (7.1)		P014
Incre ased ASAT	Outcome in one phase III trial	n/N (%)	IMI/REL 31/266 (11.7)	PIP/TAZ 20/269 (7.4)		P014

Abbreviations: EFU, early follow-up; MITT, modified intention to treat; PTA, probability of target attainment

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite recent advances in the development of antibacterial agents there is still an unmet need of agents with an acceptable safety profile that are active against carbapenem-resistant Gram-negative organisms. In the initial marketing authorisation application evaluation, it was concluded that REL can protect IMI from inactivation of Class A and C carbapenemases in Enterobacterales and *P. aeruginosa* in the absence of other types of carbapenem resistance. Because aerobic Gram-negative organisms are among the most common pathogens to cause HAP/VAP, IMI/REL could be a useful combination in the treatment armamentarium.

Treatment of HAP and VAP with or without associated bacteraemia are approved indications for IMI without the addition of REL (Article 30 referral; reference number EMEA/H/A-30/001187). Therefore, the favourable effects of IMI for the treatment of HAP/VAP with or without associated bacteraemia are already established. Notably, the "bacteraemia indication" are only considered acceptable for a new antibacterial agent in combination with an old agent already having this amendment in association with site-specific indications. Because the P014 study did not specifically enrol infections due to organisms that were resistant to IMI but susceptible to IMI/REL the acceptance of the applied indications for Recarbrio is dependent on PK/PD considerations to demonstrate that the dose of REL is sufficient to protect IMI from hydrolysis of relevant beta-lactamases in HAP/VAP with or without associated bacteraemia. The PTA analyses and ELF penetration data in healthy subjects supports the dose regimens of REL in combination with IMI for the treatment of HAP/VAP with or without concomitant bacteraemia.

The safety database for this application consists of a significant number of subjects with a high incidence of comorbid diseases receiving multiple treatments. It is therefore challenging to determine the association with a reported AE and the study drug. However, no ADRs not already known to be associated with IMI/REL were observed during this phase III trial and in general it appears that the safety profile is acceptable and comparable to what is known for IMI alone and to what was observed at the first authorisation for IMI/REL.

3.7.2. Balance of benefits and risks

Overall, the benefit risk balance of Recarbrio for the treatment of HAP, including VAP with or without associated bacteraemia is positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Recarbrio is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP), with or without concurrent bacteraemia in adults for Recarbrio; as

a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.
Furthermore, the Marketing authorisation holder (MAH) made editorial corrections and brought the PI in line with the latest QRD template version 10.1.

Version 2.0 of the RMP is approved with this variation.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Recarbrio-H-C-004808-II-0001'