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EMA/7621/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Recarbrio

International non-proprietary name: imipenem / cilastatin / relebactam

Procedure No. EMEA/H/C/004808/0000

Note

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

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

Table of contents

1. Background information on the procedure 7
1.1. Submission of the dossier 7
1.2. Steps taken for the assessment of the product 8

2. Scientific discussion 9
2.1. Problem statement 9
2.1.1. Disease or condition 9
2.1.2. Epidemiology 9
2.1.3. Aetiology and pathogenesis 10
2.1.4. Clinical presentation, diagnosis 10
2.1.5. Management 10
2.2. Quality aspects 12
2.2.1. Introduction 12
2.2.2. Active Substance 12
2.2.3. Finished Medicinal Product 20
2.2.4. Discussion on chemical, pharmaceutical and biological aspects 23
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 24
2.2.6. Recommendations for future quality development 24
2.3. Non-clinical aspects 24
2.3.1. Introduction 24
2.3.2. Pharmacology 24
2.3.3. Pharmacokinetics 26
2.3.4. Toxicology 29
2.3.5. Ecotoxicity/environmental risk assessment 34
2.3.6. Discussion on non-clinical aspects 35
2.3.7. Conclusion on the non-clinical aspects 39
2.4. Clinical aspects 40
2.4.1. Introduction 40
2.4.2. Pharmacokinetics 41
2.4.3. Pharmacodynamics 54
2.4.4. Discussion on clinical pharmacology 74
2.4.5. Conclusions on clinical pharmacology 82
2.5. Clinical efficacy 83
2.5.1. Main study 83
2.5.2. Discussion on clinical efficacy 98
2.5.3. Conclusions on the clinical efficacy 102
2.6. Clinical safety 102
2.6.1. Discussion on clinical safety 112
2.6.2. Conclusions on the clinical safety 114
2.7. Risk Management Plan 114
2.8. Pharmacovigilance 114

2.9. New Active Substance 114
2.10. Product information 115
2.10.1. User consultation 115
2.10.2. Labelling exemptions 115
2.10.3. Additional monitoring 115

3. Benefit-Risk Balance 115
3.1. Therapeutic Context 115
3.1.1. Disease or condition 115
3.1.2. Available therapies and unmet medical need 116
3.1.3. Main clinical studies 116
3.2. Favourable effects 116
3.3. Uncertainties and limitations about favourable effects 117
3.4. Unfavourable effects 118
3.5. Uncertainties and limitations about unfavourable effects 119
3.6. Effects Table 119
3.7. Benefit-risk assessment and discussion 120
3.7.1. Importance of favourable and unfavourable effects 120
3.7.2. Balance of benefits and risks 120
3.8. Conclusions 121

4. Recommendations 121

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AmpC	a class C chromosomal β-lactamase responsible for resistance in a majority of imipenem-resistant *Pseudomonas aeruginosa*
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARC	Augmented renal clearance
ASaT	all subjects as treated
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC0-24hr	area under the plasma concentration-time curve from zero to 24 hours
AUC/MIC	area under the plasma concentration-time curve normalized by the minimum inhibitory concentration
BLI	β-lactamase inhibitor
Cavg	average concentration
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cIAI	complicated intra-abdominal infection
CIL	cilastatin
CLSI	Clinical and Laboratory Standards Institute
CMS	colistimethate sodium
CQAs	Critical Quality Attributes
CR	carbapenem-resistant
CrCl	creatinine clearance
CSR	Clinical Study Report
cUTI	complicated urinary tract infection
CYP	cytochrome P450
DABCO	diazobicyclooctane
DCIV	discontinuation of IV trial treatment
DDI	drug-drug interaction
DMC	data monitoring committee
DoE	Design of Experiments
ECDC	European Centre for Disease Prevention and Control
ECI	event of clinical interest
EDC	electronic data capture
ELF	epithelial lining fluid
EFU	early follow-up
EMA	European Medicines Agency
EOT	end of therapy
ESBL	extended spectrum β-lactamase
ESRD	end –stage renal disease

EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
*f*AUC/MIC	unbound area under the plasma concentration-time curve normalized by the minimum inhibitory concentration
*f*AUC0-24hr	unbound area under the plasma concentration-time curve from zero to 24 hours
*f*AUC0-24hr/MIC	unbound area under the plasma concentration-time curve from zero to 24 hours normalized by the minimum inhibitory concentration
*f*T>MIC	time unbound concentration is above the minimum inhibitory concentration
FDA	Food and Drug Administration
FDC	fixed-dose combination
GC	gas chromatography
GCP	Good Clinical Practice
HABP	hospital-acquired bacterial pneumonia
HDPE	high density polyethylene
HF / HFIM	hollow fiber (*in vitro* infection model)
HPLC	High performance liquid chromatography
IAI	intra-abdominal infection
IBD	International birth date
ICH	International Conference on Harmonization
ICU	intensive care unit
IMI	imipenem/cilastatin
IMI/REL	fixed-dose combination of imipenem/cilastatin/relebactam (MK-7655A)
IPM	imipenem
IR	infrared spectroscopy
ISM	Integrated Summary of Microbiology
IV	intravenous
KF	Karl Fischer titration
KPC	*Klebsiella pneumoniae* carbapenemase
LDPE	low density polyethylene
LRTI	lower respiratory tract infection
MATE	multidrug and toxin extrusion protein
MDR	multi-drug resistant
ME	microbiologically evaluable
MFD	maximum feasible dose
MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration at which half 50% of isolates inhibited
MIC_{90}	minimum inhibitory concentration at which half 90% of isolates inhibited
MITT	microbiological intent-to-treat
mMITT	microbiological modified intent-to-treat
MS	mass spectrometry
NDA	New Drug Application
NMR	nuclear magnetic resonance spectroscopy
OAT	organic anion transporter
OprD	imipenem entry porin
OTX	on-therapy

OXA	oxacillinase
p	p-value
PAE	post-antibiotic effect
PD	pharmacodynamic
PDC	Pseudomonas-derived cephalosporinase
% *f*T>MIC	percentage of time unbound concentration is higher than MIC
PDT	pharmacokinetic-pharmacodynamic target
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PSUR	periodic safety update report
PTA	probability of target attainment
QC	quality control
QTc	corrected QT interval
REL	relebactam (MK-7655)
RH	Relative humidity
RI	Renal impaired / impairment
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMART	Study for Monitoring Antimicrobial Resistance Trends
SmMITT	supplemental microbiological modified intent to treat
SmPC	Summary of Product Characteristics
t1/2	terminal half-life
TPKPD	translational pharmacokinetic/pharmacodynamic
ULN	upper limit of normal
UN	United Nations
US	United States
USP	United States Pharmacopoeia
USPI	United States Package Insert
UV	ultra-violet spectrometry
V1	central volume of distribution
VABP	ventilator-associated bacterial pneumonia
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme B.V. submitted on 9 November 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Recarbrio, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 April 2017.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P0163/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP 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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance relebactam contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP on the development for the indication from the CHMP on 26 February 2015 (EMEA/H/SA/2974/1/2014/III), 13 October 2016 (EMEA/H/SA/2974/2/2016/II) and 23 February 2017 (EMEA/H/SA/2974/2/FU/1/2016/I). The Scientific advice pertained to the following aspects:

On 26 February 2015 the applicant received initial Scientific Advice on:

- The non-clinical ADME/PK, toxicology, safety pharmacology, developmental and reproductive toxicity program to support registration of the combination of IMI and relebactam
- Human ADME, clinical pharmacology and safety pharmacology studies
- The Phase 3 trial evaluating IMI + Relebactam in patients with hospital-acquired pneumonia and ventilator-associated pneumonia, complicated intra-abdominal infections, and complicated urinary tract infections due to imipenem-resistant organisms
- The Phase 3 trial evaluating IMI + Relebactam in patients with hospital-acquired pneumonia and ventilator-associated pneumonia
- The Adequacy of the phase 2 and phase 3 studies to support full approval for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia and for the treatment of serious bacterial infections caused by known or clinically suspected carbapenem-resistant (CR) pathogens in patients with limited treatment options
- The safety database
- The need for additional clinical or observational studies post-approval

On 13 October 2016 a second advice was received on:

- Starting materials
- The use of of using aseptic processing instead of terminal sterilization
- The ERA strategy to support registration of the product

On 15 December 2016 the third advice was received on:

- The qualification strategy for the powder for injection degradation products
- Process validation strategy for the powder for injection manufacturing process

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: Alar Irs

The application was received by the EMA on	9 November 2018
The procedure started on	29 November 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 February 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	25 February 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 March 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 March 2019
The applicant submitted the responses to the	16 August 2019

CHMP consolidated List of Questions on	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	10 October 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	17 October 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	07 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	05 December 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Recarbrio on	12 December 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Imipenem/cilastatin/relebactam is proposed by the Applicant to be indicated for the treatment of infections due to aerobe Gram-negative microorganisms in adults with limited treatment options.

2.1.2. Epidemiology

Infections caused by multidrug-resistant (MDR) bacteria continue to increase and limit the utility of existing antibacterial agents. Data from the US Centres for Disease Control and Prevention (CDC) report more than 2 million cases of infection with resistant bacteria and at least 23,000 associated deaths in the United States every year (CDC 2013). 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, was highest among infants and the elderly and was highest in Italy and Greece. Carbapenem-resistance (CR) in *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* contributed significantly to the number of estimated deaths (approximately 4,000 and 2,000, respectively) whereas the numbers of deaths estimated to be caused by infections caused by CR *Escherichia coli* was lower (~100) reflecting the lower incidence of CR in this species. 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-beta-lactamase (NDM) and Verona integron-encoded metallo-β-lactamase (VIM) were detected to a lesser extent.

2.1.3. Aetiology and pathogenesis

Multi drug resistant (MDR) Gram-negative organisms such as CR *P. aeruginosa* and Enterobacteriaceae are important pathogens in complicated urinary tract infections (cUTI) including pyelonephritis, complicated intra-abdominal infections (cIAI) and hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP) i.e. infections that are commonplace. Complicated UTIs are UTIs complicated by involvement of the upper urinary tract (pyelonephritis) or by underlying functional or anatomic abnormalities of the urinary tract. Common uropathogens causing cUTI are *E. coli*, other Enterobacteriaceae and *P. aeruginosa*. Complicated IAI is defined as the extension of an IAI beyond the organ of origin, causing peritonitis or abscess formation. Complicated IAIs are usually polymicrobial in nature and the major pathogens involved are usual residents of the gastrointestinal tract, including Enterobacteriaceae, streptococci, and certain anaerobes (particularly *Bacteroides fragilis*) but *P. aeruginosa* is also commonly encountered. HAP and VAP are, by definition, infections in hospitalised (or recently hospitalised) patients. Colonisation of the respiratory tract with a variety of Gram-positive and Gram-negative bacteria may lead to infection. Among the most commonly encountered pathogens in HAP/VAP are *Staphylococcus aureus*, Enterobacteriaceae and *P. aeruginosa*.

2.1.4. Clinical presentation, diagnosis

Infections typically caused by aerobic Gram-negative organisms (cUTI, cIAI and HAP/VAP) are diagnosed based on clinical presentations and radiologic imaging in addition to microbiological investigations to characterise the pathogens causing the infections.

2.1.5. Management

Beta-lactam antibacterial agents are commonly used to manage infections when they involve Gram-negative pathogens. Increasing resistance to beta-lactams, including the carbapenems, has led to some organisms being effectively untreatable or treatable only with resource to colistin with or without other agents to which they remain at least partly susceptible. Treatment emergent nephrotoxicity is of concern for colistin. Fosfomycin is active against beta-lactamase producing bacterial strains. However, clinical data on the treatment of MDR bacterial infections with fosfomycin are limited. Tigecycline is another option for the treatment of beta-lactam-resistant Gram-negative infections. However, tigecycline is not active against *Pseudomonas* spp. Moreover, safety concerns of an increased risk of death with tigecycline have limited its use. Newer beta-lactam/beta-lactamase (BL/BLI) combinations such as ceftolozane/tazobactam,

ceftazidime/avibactam and meropenem/vaborbactam are possible options for the treatment of some carbapenem resistant Gram-negative organisms but none of them are universal or active against class B (metallo-beta-lactamase) producers. Overall, there is still a high unmet medical need for additional antibacterial agents addressing carbapenem resistance in Gram-negative organisms.

About the product

Imipenem (IPM) 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. IPM 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 IPM. CIL does not have antibacterial activity. IMI (imipenem-cilastatin) has been authorised and used in the EU since the 1980s. It has a spectrum that includes Gram-positive, Gram-negative and anaerobic bacteria. It is given intravenously at doses up to 1 g q6h.

Relebactam (REL) is a novel 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 no intrinsic significant antibacterial activity at clinically relevant doses. The role of REL in the FDC is to restore the activity of IPM in IPM-resistant gram-negative infections when the resistance is caused by production of β-lactamases within the spectrum of REL´s inhibitory activity.

Imipenem/cilastatin/relebactam is proposed by the Applicant to be indicated for the treatment of infections due to aerobic Gram-negative microorganisms in patients 18 years of age and older with limited treatment options.

The proposed posology is 500/500/250 mg q6h in patients with a creatinine clearance greater than or equal to 90 mL/min. Dosage adjustments are recommended in patients with renal impairment.

Recarbrio is for intravenous use.

Type of Application and aspects on development

The CHMP did not agree to the applicant’s request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that although Recarbrio may have a somewhat different spectrum compared with recently approved β-lactam/β-lactamase inhibitor (BL/BLI) combinations, it does not represent a major therapeutic innovation per se.

2.2. Quality aspects

2.2.1. Introduction

Imipenem/cilastatin/relebactam is a parenteral (IV) fixed dose combination (FDC) of relebactam, combined with imipenem/cilastatin developed by the Applicant for the treatment of serious infections caused by carbapenem-resistant gram-negative bacteria.

The finished product is supplied as is a parenteral fixed dose combination (FDC) presented powder for solution for infusion containing cilastatin, imipenem and relebactam as active substances in a vial. Each vial contains imipenem monohydrate equivalent to 500 mg of imipenem anhydrate, cilastatin sodium salt equivalent to 500 mg of cilastatin and relebactam monohydrate equivalent to 250 mg of relebactam anhydrite.

The finished product is packaged in a 20 mL glass vial with a 20 mm rubber stopper and an aluminum flip-off seal.

2.2.2. Active Substance

Imipenem

General information

The chemical name of imipenem is (5R,6S)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid. It corresponds to the molecular formula $C_{12}H_{17}N_3O_4S \bullet H_2O$, its relative molecular mass is 317.37 and it has the structure shown in *Figure 1*. Imipenem is a known active substance that has Ph. Eur. monograph available. Full information has been presented in the dossier concerning the manufacture of the active substance.

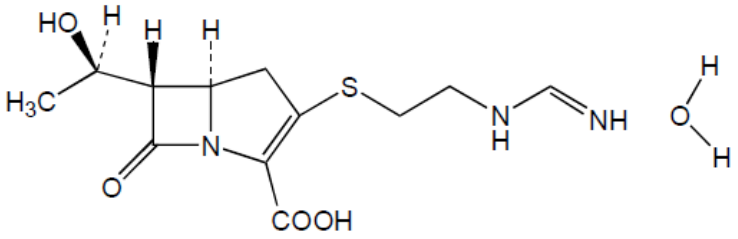


Figure 1. Structure of imipenem monohydrate.

The structure of the active substance (AS) was elucidated by a combination of ultra-violet spectrometry (UV), infrared spectroscopy (IR) and ^{13}C- and ^{1}H- nuclear magnetic resonance spectroscopy (NMR). The provided information supports the proposed structure of the substance and is considered acceptable for this compendial active substance.

Imipenem monohydrate is a white or almost white or pale yellow powder, slightly hygroscopic substance. It is slightly soluble in water and methanol. The pKa values for imipenem have been determined by aqueous acidic/basic potentiometric titration at 25°C. The respective pKa1 and pKa2 are ~3.2 and ~9.9.

The molecule has three chiral centres and is optically active. All three stereogenic centre centres for imipenem originate from a starting material, the chiral purity of which is controlled by HPLC methods, which ensure control of potential chiral isomer impurities. Imipenem has only one known crystal form.

Manufacture, characterisation and process controls

The synthesis is described in nine overall steps, eight of which comprise actual synthetic steps (bond breaking/formation) and the last an aseptic sterilisation step.

The starting materials of imipenem sterile have been redefined following a request by the CHMP. The new proposed starting materials are considered acceptable according to the requirements of ICH Q11. Acceptable specifications have been set and the analytical methods used in the analysis of the starting materials have been described sufficiently.

Critical process parameters with adequate limits have been identified. The in-process controls and their respective methods have been indicated and included in the relevant sections of the updated Module 3. Non isolated intermediates have been indicated and their control criteria for the use in next step specified.

A discussion on the potential genotoxic impurities of the active substance was not provided. This is considered acceptable as the impurities from this route of synthesis are qualified by use. The control of residual solvents used in the process and possibly present as contaminants in the reagents used and in the designated starting materials has been discussed and included in the risk assessment of the starting materials and the proposed control strategy is acceptable.

The description of the sterilisation process has been provided with sufficient detail. The validation study for sterile imipenem was completed on three production scale batches. The presented validation data for the process for the critical process steps are acceptable.

The active substance packaging has been described.

The packaging cans are sterilised and depyrogenated via a sufficiently described process. The PTFE used in manufacture of the gasket meets the EU foodstuff requirements of the regulation 10/2011, regulation 1169/2011 for materials intended to come into contact with food.

Specification

Imipenem monohydrate (sterile) active substance specification includes appropriate tests and limits for assay (Ph. Eur.), bacterial endotoxins (Ph. Eur.), related substances (Ph. Eur.), appearance of solution (Ph. Eur.), identity (Ph. Eur.), water content (Ph. Eur.), specific rotation (Ph. Eur.), sulfated ash, pH (Ph. Eur.), sterility (Ph. Eur.), appearance characteristics (visual), residual solvents (GC), heavy metals (USP) and crystallinity (Optical Microscopy).

The acceptance criteria and analytical methods for sterile imipenem are in line with the Ph. Eur. and include additional tests are performed to ensure the quality of the active substance. The control of impurities is in line with the Ph. Eur. monograph.

An elemental impurity risk assessment was performed for the finished product (see below "Product Specification"), as per ICH Q3D. For all elemental impurities the results were either less than the limit of detection or not detected at all. Consequently, no routine testing of elemental impurities in the active substance specification is required.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from three recently manufactured batches of imipenem sterile active substance were provided. All results met the acceptance criteria and consistent quality of the active substance has been demonstrated.

Stability

Stability data on three commercial scale batches of active substance stored in the intended commercial packaging or equivalent for to 36 months under long term conditions 5°C ± 3°C/ambient humidity was provided according to the ICH guidelines.

Parameters investigated: appearance characteristics, assay, impurities and water content. Results were within the specifications. No trends were observed.

Stability studies of non-sterile imipenem at accelerated short term conditions of 25°C/60% RH have been completed to assess the impact of excursions during transportation to the sterilisation site. Non-sterile imipenem has been shown to be suitably stable for up to 7 days under conditions up to 25°C/60% RH to support limited excursions outside of refrigeration.

No stressed or accelerated stability studies have been performed in accordance with ICH Q1A to cover shipment, and subsequent use. The finished product manufacturing is performed at the same manufacturing site as the sterile imipenem is produced. Since no transportation of sterile imipenem will take place, this is acceptable. In addition, the applicant committed that formal accelerated stability studies at 25°C ± 2°C/60% RH ± 5% RH are planned for sterile imipenem for 6 months as per ICH; this together with the storage statement for imipenem, sterile and non-sterile, 'Store and transport refrigerated' which has been included in the documentation is considered acceptable.

Forced or photostability studies have not been performed, which is acceptable because according to the Ph.Eur. monograph the substance is not light sensitive.

Based on the data provided, a retest period of 36 months for sterile Imipenem when stored at 5 °C ± 3 °C /Ambient Humidity is acceptable.

Cilastatin

General information

The chemical name of cilastatin is [Sodium (Z)-7-[[(R)-2-amino-2-carboxyethyl]thio]-2-[(S)-2,2-dimethylcyclopropanecarboxamido]-2-heptenoate. It corresponds to the molecular formula $C_{16}H_{25}N_2NaO_5S$,

its relative molecular mass is 380.44 and it has the structure shown in *Figure 3*. Cilastatin is a known active substance that has Ph. Eur. monograph available. Full information has been presented in the dossier concerning the manufacture of the active substance.

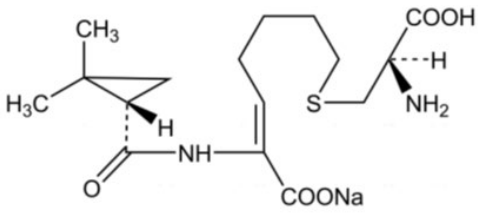


Figure 2. Structural formula of cilastatin sodium

The molecular structure of cilastatin was elucidated by a combination of the following methods; ultra-violet spectrometry (UV), infrared spectroscopy (IR) and ^{13}C- and ^{1}H- nuclear magnetic resonance spectroscopy (NMR). The provided information supports the proposed structure of the substance and is considered acceptable for this compendial active substance.

Cilastatin sodium is an off-white to white hygroscopic amorphous powder, which is very soluble in water and methanol. The molecule contains two chiral centers and is optically active. Cilastatin sodium is fully amorphous, and no crystal forms have been identified.

Manufacture, characterisation and process controls

The synthesis is described in seven overall steps, six of which comprise actual synthetic steps (bond breaking/formation) and the last an aseptic sterilisation step. The starting materials of cilastatin sodium sterile have been redefined upon the request of the CHMP. The new proposed starting materials have been satisfactorily justified in line with ICH Q11 and are considered acceptable.

The critical process parameters, in-process controls and their control methods have been updated and are considered acceptable. The acceptance criteria for raw materials used in cilastatin sodium sterile active substance process have also been updated following the redefinition of the starting materials.

Cilastatin sodium non-sterile intermediate (CNS) specifications have been updated and respective methods have been also described.

Information on the quality and control of non-isolated intermediate was provided, whereas for the isolated intermediate downstream controls confirm appropriate process characterization and robustness therefore no further quality control or in-process requirements are required for the isolated intermediate; this is considered sufficient based on long-term experience in the manufacture of cilastatin sodium. These tests and the associated control strategy ensure that cilastatin sodium active substance meets its critical quality attributes. Overall the synthesis process can be considered acceptable.

A comprehensive discussion on potential impurities that may be present in cilastatin sodium sterile based on the commercial manufacturing process, including reaction process-related impurities, synthetic intermediates, raw materials, potential stereoisomers (when applicable), compounds which may form as a result of degradation has been provided. The control strategy applied for impurities originating from starting materials has been justified and can be accepted. Overall the presented discussion of the fate and the purge of impurities can be considered acceptable to assure the purity of cilastatin sodium sterile.

An adequate overview of the validation of sterilisation process critical points have been provided, including sterilisation of cilastatin manufacturing process equipment and components, sterilisation of containers, validation, and process simulations. The description of the sterilisation process has been provided with sufficient detail. The process validation study for sterile cilastatin was completed on three production scale batches. The presented validation data for the process for the critical process steps are acceptable.

The active substance packaging has been described.

The packaging cans are sterilised and depyrogenated via a sufficiently described process. The PTFE used in manufacture of the gasket meets the EU foodstuff requirements of the regulation 10/2011, regulation 1169/2011 for materials intended to come into contact with food.

Specification

Cilastatin sodium (sterile) active substance specification includes appropriate tests and limits for assay (Ph. Eur.), related substances (Ph. Eur.), residual solvents (GC), water content (Ph. Eur.), heavy metals (Ph. Eur.), degree of colouration (Ph. Eur.), specific rotation (Ph. Eur.), identity (Ph. Eur.), sodium precipitation (Ph. Eur.), opalescence (Ph. Eur.), pH (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

The active substance specifications comply with the current Ph. Eur. Monograph. Additional non-compendial specifications were established after review of the capabilities of the analytical methodology and data generated on production batches. Two additional impurities have been included to the list of impurities Specified impurities level is not in line with ICH Q3A, however, it is considered toxicologically qualified by use.

No elemental impurities are used in the manufacture of starting materials. Risk assessment according to ICH Q3D has been provided under finished product section (see below "Product Specification"). In addition, Class 1, 2A and 3 metals were investigated in non-sterile cilastatin sodium. Based on these results, it can be concluded that there is no need to specify any elemental impurities in the specification of cilastatin active substance.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analytical data from three production scale batches from the final sterile active substance manufactured by the proposed manufacturer have been provided. All results met the acceptance criteria and consistent quality of the active substance has been demonstrated.

Stability

Stability data on three commercial scale batches of active substance stored in the intended commercial packaging or equivalent for up to 18 months under long term conditions 5°C ± 3°C/ambient humidity was provided according to the ICH guidelines.

Parameters investigated: appearance characteristics, assay, impurities and water content. Results were within the specifications. No trends were observed.

Cilastatin non-sterile is shipped; the shipping condition is supported by accelerated stability, which demonstrated modest increases in impurities and increases water content; no meaningful impact on cilastatin quality is anticipated during brief excursions above refrigerated storage conditions.

No formal accelerated stability study was performed for sterile cilastatin sodium. It has been confirmed that sterile cilastatin sodium is not transported after sterilisation since the finished product manufacturing is performed at the same manufacturing site. In addition, the applicant committed that formal accelerated stability studies at 25°C ± 2°C/60% RH ± 5% RH are planned for sterile cilastatin for 6 months as per ICH. It has been confirmed that cilastatin sodium sterile will not be transported, therefore it is accepted that no additional storage statement is included covering transportation.

No photostability or accelerated humidity studies were presented. As, according to Ph. Eur. monograph, cilastatin sodium is not light sensitive, the omission of photostability studies is considered acceptable.

A retest period of 18 months when stored at 5°C ± 3°C/ambient humidity is accepted for the sterile substance.

Relebactam

General information

The chemical name of relebactam hydrate is [(1R,2S,5R)-7-Oxo-2-(piperidin-1-ium-4-ylcarbamoyl)-1,6-diazabicyclo[3.2.1]octan-6-yl sulfate hydrate. It corresponds to the molecular formula $C_{12}H_{20}N_4O_6S \cdot H_2O$, its relative molecular mass is 366.4 and it has the structure shown in Figure 5.

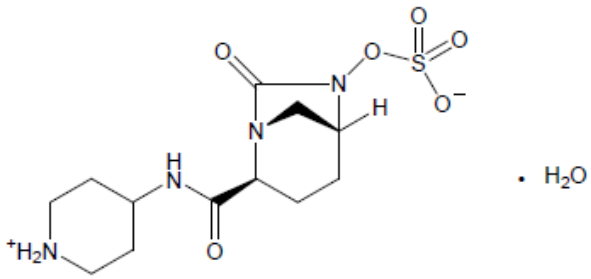


Figure 3. Structural formula of relebactam hydrate

The structure of the active substance was elucidated by a combination of ultra-violet spectrometry (UV), infrared spectroscopy (IR), mass spectrometry (MS), ^{13}C- and ^{1}H- nuclear magnetic resonance spectroscopy (NMR) and X-ray powder diffraction.

Relebactam is a white to off-white hygroscopic crystalline powder. It is freely soluble in water, practically insoluble in isopropyl acetate, isopropyl alcohol, and acetonitrile and very slightly soluble in methanol.

It has three stereogenic centers. The stereocenters in relebactam are controlled in the starting material and/or defined during the synthesis. Chiral purity is controlled by a chiral HPLC method.

Different polymorphs of relebactam were identified during polymorph screening and development. During routine relebactam manufacturing, the crystalline monohydrate is isolated exclusively from the commercial process.

Based on the information provided by the applicant, relebactam is considered to be a new active substance (NAS).

Manufacture, characterisation and process controls

Relebactam monohydrate is obtained by 8 overall steps, seven of which comprise actual synthetic steps (bond breaking/formation) and the last an aseptic sterilisation step.

An enhanced development program was executed in accordance with ICH Q9 and ICH Q11 for the manufacturing process of relebactam. Manufacturing operations perceived as a higher risk of impacting Critical Quality Attributes (CQAs) or more likely to have multifactor interactions were studied in a systematic way by utilizing multifactor Design of Experiments (DOE) studies, first principles, prior knowledge, or a combination of these elements. Operations presenting lower risk or not expected to have multifactor interactions were studied with a traditional One Factor at A Time (OFAT) approach. The development studies led to the definition of the proven acceptable ranges for the manufacturing process. A design space is not claimed but instead ranges have been identified for operating parameters and conditions.

The proposed commercial manufacturing process is described as Route 2. Earlier in the development a manufacturing route designated as 'Route 1' was used. The batches of relebactam manufactured according to 'Route 1' have been used in pre-clinical, early clinical (Phase I and II), and safety studies. The details of process development history were provided.

The characterisation of the AS and its impurities are in accordance with the EU guideline on chemistry of new active substances. Impurities that may be present in the starting materials or intermediates were assessed for their impact on the downstream intermediates and on the quality of the relebactam active substance. The fate and purge of starting material and intermediates impurities are well understood and these impurities are controlled with individual impurity specifications which were set considering the fate and purge as well as the range of each impurity observed at pilot and commercial scale.

The aseptic manufacturing process step has been justified and validation of the process has acceptably completed on three production scale batches.

Relebactam is packaged in in a can sealed with a stopper with an. As no guidelines are established for quality requirements of metal containers the presented information can be accepted. The stopper complies with Ph. Eur. monograph 3.2.9. and an adequate specification has been provided.

The primary relebactam packaging components are sterilised using a well described process. Non-sterile bulk is packaging has been described. The liner complies with Ph. Eur. monograph 3.1.4. The information on container-closure system used for non-sterile bulk is limited but can be accepted.

Specification

Relebactam monohydrate (sterile) active substance specification includes appropriate tests and limits for description (visual), assay (HPLC), impurities (HPLC), specific rotation (polarimetry), residual solvents (GC), water content (Ph. Eur.), identity (IR), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

The applied limits for each identified impurity have been justified adequately based on batch analysis data and toxicologically qualified. The limit for unidentified impurities is established in line with the ICH Q3A requirements.

Evaluation and control of potential mutagenic impurities (PMI) was performed in accordance with ICH M7. The manufacturing process from the starting materials to the active substance was evaluated for potential formation of mutagenic impurities. In addition, two steps of the starting material manufacturing process were also evaluated for mutagenic impurities. The acceptable intake was calculated based on maximum 1000 mg/day dose (MDD). As the active substance is in hydrate form, the correct MDD is 1052 mg/day, however as the active substance is intended for short term use only to treat life-threatening conditions, the slight difference in calculated TTC value is not raised as a concern and the provided data is considered acceptable.

A quality risk management approach, as per ICH 3QD, was conducted. Analysis of four batches manufactured, using the commercial process showed that levels of all Class-1 and Class-2A elements were less than 30% of the permitted daily exposure. Palladium was not detected (< 0.1ppm) in these batches but is controlled in an intermediate. Hence a test for elemental impurities is not considered necessary for release of active substance.

Justifications for omitting tests for physical characteristics (polymorphic form or particle size distribution) based on batch data are also considered acceptable.

Batch analyses data from 18 batches of relebactam used in clinical studies, safety studies and formal stability studies were provided. These include batches of relebactam using the former Route 1 and the remaining batches manufactured using the proposed Route 2 at commercial scale. The batch analysis data presented are within the acceptance criteria and confirm consistent active substance quality.

Stability

Stability data on four commercial scale (Route 2) batches of active substance stored in the intended commercial packaging for up to 36 months under long term conditions (25 °C / 60% RH), and for 6 months under accelerated conditions (40 °C / 75% RH) was provided according to the ICH guidelines.

Parameters investigated: description, assay and impurities and water content. The analytical methods used for stability studies were the same as those provided at release. No significant changes were observed in any of the monitored parameters in any of storage conditions mentioned above.

Forced degradation studies

Additionally, forced stress studies were conducted under acidic, basic, oxidative, photolytic, and thermal stress conditions to induce the formation of potential degradation products and demonstrate the stability indicating nature of the HPLC analytical procedures. Significant degradation occurred under acidic and caustic stress conditions. Minor degradation was observed under free radical oxidation stress; no degradation was observed under photolytic and thermal stress conditions. The stability indicating nature of the assay and impurity method has been sufficiently demonstrated.

Photostability

Relebactam was also subjected to visible light and near ultra-violet light stress conditions according to the confirmatory conditions of ICH Q1B to demonstrate photostability of the active substance. The results from this study showed that relebactam is not susceptible to photo-degradation.

Based on the provided data, the proposed retest period of 24 months for the active substance when stored in the proposed primary packaging without any special storage conditions, is considered acceptable

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is supplied as Imipenem/ Cilastatin /Relebactam powder for solution for infusion in a glass vial. Each vial of the finished product contains imipenem monohydrate to provide 500 mg of imipenem anhydrate equivalent, cilastatin sodium salt to provide 500 mg of cilastatin equivalent, relebactam monohydrate to provide 250 mg of relebactam anhydrate equivalent. The product contains 37.5 mg of sodium (1.6 mEq).

The primary strategy of the finished product development program was to provide a chemically stable formulation with sterility assurance, while capitalising on the extensive manufacturing experience from the already authorised Cilastatin/Imipenem Intravenous Injection (Tienam). Cilastatin/Imipenem Intravenous Injection contains two of the three active substances, namely, imipenem and cilastatin.

The Quality Target Product Profile (QTPP) was defined and presented. Based on the QTPP the product critical Quality attributes have been determined.

The finished product is presented as a combination of three sterile active substances and one sterile excipient in a single vial. The stability of the active substances drove the choice of the specific pharmaceutical form and the excipients. Sterilisation of excipients was sufficiently described. The different formulations used in early clinical development have been described. The final market formulation combined sterile relebactam with sterile imipenem/cilastatin into a single vial. This formulation was used to support Phase III trials, formal stability studies and commercial product. The choice of the sterilisation method has been well justified.

Compatibility with Diluents

Batches of the finished product (one from the beginning and one towards the end of its shelf-life) have been subjected for compatibility studies with three commonly used diluents; 0.9% Sodium Chloride Injection; 5% Dextrose Injection; and mixture of 5% Dextrose and 0.9% Sodium Chloride Injection. Based on the available in-use study results, the product is unstable when reconstituted and diluted in proposed diluents in refrigerated or room temperature conditions. In all media a decrease in assay of imipenem and an increase in impurities were observed. Several degradation products, unique to the reconstituted and diluted product, arise in the admixture solutions. These impurities are not listed in the finished product specification because these are not relevant in the dry powder formulation. According to the applicant, the degree of degradation for imipenem and cilastatin in 5% Dextrose Injection or in 0.9% Sodium Chloride Injection is similar to what was observed in the Tienam admixture solutions using the same diluents. In support of the claim, satisfactory comparative in-use stability results of current product with Tienam at release and the end of shelf-life has been presented within 2 hours in room temperature. The applicant aligns with the SmPC of Tienam, i.e., the diluted solutions should be used immediately, and the time interval between the beginning of reconstitution and the end of intravenous infusion should not exceed two hours. The product information has been amended accordingly.

As already agreed in connection with Tienam product, the use of 5% glucose should be restricted to exceptional circumstances where 0.9% sodium chloride cannot be used for certain patients. The product information has been amended accordingly to reflect this.

Compatibility with administrative devices materials and with other injectable drug products mentioned in the product information has also been demonstrated.

The finished product is packaged in glass vial, with stopper, and a seal with flip-off cap are suitable for their intended use. The primary packaging material complies with Ph. Eur.

Manufacture of the product and process controls

The finished product manufacturing process consists of standard unit operations and equipment for sterile powder production, and comprises the following steps: aseptic consolidation, blending and aseptic filling and sealing into a vial followed by inspection. The manufacturing process for Cilastatin/Imipenem/ Relebactam powder for solution for infusion uses conventional manufacturing techniques and equipment.

Critical steps of the finished product manufacturing process have been defined and are controlled by suitable in-process controls. A bulk hold time has been established.

Sterile Sodium Bicarbonate Manufacture
Sterile sodium bicarbonate is produced via a process which has been described in sufficient detail and is controlled by appropriate controls and has been satisfactorily validated.

The aseptic vial filling process has been successfully validated.

The manufacturing process for Recarbrio powder for solution for infusion uses conventional manufacturing techniques and equipment. It is similar formulation, process, and uses the same commercial equipment as the Cilastatin/Imipenem Intravenous Injection. Based on batch analysis data gained on several pilot batches and one production batch scale and adequacy of in-process controls as well as previously experience from Cilastatin/Imipenem, it is considered acceptable that the full process validation will be performed prior to placing the product in the market is in line with the process validation guideline (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1). The validation protocol has been provided and is acceptable.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification (UV, HPLC), cilastatin assay (HPLC), imipenem assay (HPLC), relebactam assay (HPLC), cilastatin degradation products (HPLC), imipenem degradation products (HPLC), relebactam degradation products (HPLC), uniformity of dosage units (Ph. Eur.), container closure integrity (vacuum decay leak test), water content (KF), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.). The reconstituted solution is tested for completeness and clarity of solution (visual), particulate matter (Ph.Eur.), pH (Ph.Eur.) and colour (visual).

The acceptance criteria for degradation products have been established for cilastatin, imipenem, and relebactam in the finished product, in accordance with the ICH guidance Q3B Impurities in New Drug Products for a product with a maximum daily dose of 10 mg to 2 g/day.

The degradation products present in Recarbrio Powder for Injection have been qualified based on toxicology studies at levels that have demonstrated biological safety, according to ICH Q3B (R2) guidance.

According to ICH M7, no assessment of mutagenic impurities related to cilastatin sodium or imipenem is required for Cilastatin/Imipenem Intravenous Injection as it has been in the market since 1985. The only

relebactam related degradation is controlled as a regular impurity based on the negative results from AMES test.

A quality risk management approach per ICH Q3D was conducted to assess the elemental impurities (EI) in the potential sources of Cilastatin/Imipenem/Relebactam Powder for Injection finished product, including excipient, active substances, water, manufacturing equipment, and container closure system. The worst-case maximum daily exposure for each potential elemental impurity in the product was determined to be below the control threshold of 30% of the PDE. Based on the presented risk assessment summary and available results, it can be concluded that there is no need to specify any elemental impurities in the final product, in line with the above guideline.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data for 9 commercial scale batches of the finished product used in clinical and stability studies have been provided. All the test results were within the specification limits confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three commercial scale batches of finished product stored (both upright and inverted) for up to 24 months under long term conditions at 30°C/75%RH and for six months under accelerated conditions at 40°C/75%RH according to ICH guidelines have been presented.

The following parameters have been investigated: description, assay, degradation products, constitution time, colour and clarity of constituted solution, visible particles (constituted solution), pH, water, container closure integrity, particulate matter, physical stability (XRPD), sterility, and bacterial endotoxins. All results complied with the specifications. No significant stability trends were observed at any storage condition.

Statistical analysis was applied to evaluate the product shelf-life, following the principles in ICH guideline Q1E. Linear regression was performed on the formal stability study batches, using the available assay stability data at 30°C/75%RH and results suggest a shelf life of at least 30 months.

Photostability
Three commercial scale batches were subjected to photostability stress testing under the conditions of ICH Q1B, Option 2. The samples were tested for description, assay, degradation products, constitution time, colour and clarity of constituted solution, visible particles-constituted solution, pH, moisture and particulate matter. According to the photostability study, the product is demonstrated to be sensitive to light in the primary packaging. The product information has been updated accordingly.

An alternate method of calculating the expiry date has been proposed based on the bulk hold stability study to begin when the blend is dispensed for packaging, provided the blend is not held for more than 3 months prior to packaging. The proposed alternative is in line with Q & A on stability issues of pharmaceutical bulk products use in manufacture of the finished product published by EMA and is therefore acceptable. Supporting stability data for two commercial scale batches was presented. The blended product was held for a minimum of 3 months and processed into finished product, then stored 24 months at the long-term storage condition 30ºC/75% RH, and for 6 months at accelerated conditions of 40ºC/75% RH. Available results remain within the acceptance limits and no trends were observed.

In-use stability
In-use stability testing of the reconstituted finished product that was prepared and stored in accordance with the instructions was performed as part of pharmaceutical development. The study supports the diluents and conditions as stated in SmPC section 6.6.

Based on the overall stability data, the claimed shelf life of 30 months without any special temperature storage conditions and with the recommendation "Keep vials in outer carton, in order to protect from light", is acceptable (SmPC sections 6.3 and 6.4).

Post approval change management protocol

A change management protocol for relebactam has been submitted and is considered acceptable as the presented data is in line with the Q&A document EMA/CHMP/CVMP/QWP/586330/2010 requirements.

Adventitious agents

None of the materials used in the manufacture of Recarbrio are of human or animal origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

In the context of the on-going review under Article 5(3) of Regulation (EC) No 726/2004 related to the potential presence of nitrosamine impurities in human medicinal products (https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing-authorisation-holders_en.pdf, https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation_en.pdf), MAHs of products containing chemically-synthesized active substances are being asked to review their products for potential presence of nitrosamine impurities and to conduct risk evaluations/risk assessments as appropriate.
No risk evaluation has been submitted for imipenem, cilastatin and relebactam in Recarbrio within the current procedure. Therefore, it is recommended that a risk evaluation on the potential risk of presence of nitrosamine in imipenem, cilastatin and relebactam in Recarbrio is conducted after the marketing authorisation, within six months of the publication of the call for review (19th September 2019). In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within 3 years of the publication of the call for review (19th September 2019), or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to conduct formal accelerated stability studies for sterile imipenem for 6 months. In case there are any changes needed as a result, the documentation will be updated. To be submitted by the end of Q4 2020.

- to conduct accelerated stability studies for cilastatin for 6 months and make changes to the storage statement if applicable. To be submitted by the end of Q2 2021.

- it is recommended that a risk evaluation on the potential presence of nitrosamine impurities in imipenem, cilastatin and relebactam in Recarbrio is conducted after the marketing authorisation by 19 March 2020). In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods by 19 September 2022, or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant initially submitted a non-clinical overview that covered relebactam only. Responding to a CHMP request, during the assessment an updated non-clinical overview addendum regarding imipenem and cilastatin was also submitted and assessed. No new non-clinical studies were required for imipenem or cilastatin alone or in combination with relebactam.

2.3.2. Pharmacology

Primary pharmacodynamic studies

See clinical pharmacodynamics section further below.

Secondary pharmacodynamic studies

Off-target effects of relebactam (REL) were screened for in a commercially available (MDS Pharma Service) standard panel of 163 potential secondary targets with receptors, transporters, ion channels and enzymes. REL at 10-100 µM (100 µM ~2.5-fold the clinical free fraction C_{max}, 38 µM, at the RHD, 250 mg) did not

inhibit binding of any of the competitive ligands (inhibition defined as greater than 50% inhibition). For secondary pharmacodynamics evaluation of imipenem or cilastatin alone or in combination the applicant refers to the studies summarized in the safety pharmacology section.

Safety pharmacology programme

Overall, there were no REL related effects of concern in the clinically relevant dose range on cardiovascular, respiratory or CNS functions observed in the safety pharmacology *in vivo* models.

Cardiovascular effects were studied *in vitro* and *in vivo* under GLP conditions. In a whole-cell voltage-clamping of CHO cells stably expressing hERG, REL had no significant effect on hERG current relative to time-dependent changes observed in the vehicle control, at a maximal testable actual concentration of 318 µM (~8-fold clinical free fraction C_{max}, 38 µM). In a monkey telemetry study, no effects were observed on QT/QTc interval at C_{max} (4460 µM) which was ~96-fold the clinical C_{max}. In addition, there were no effects on haemodynamics (arterial blood pressure and heart rate) or on respiratory function or body temperature. The NOAEL was at highest dose tested, 225 mg/kg.

Neurobehavioural effects of REL were studied by a Functional Observational Battery (FOB) carried out as a separate part, on 6 male rats/dose at 50, 150 and 450 mg/kg on day 1, in a one-month IV toxicity GLP study. There were no REL-related neurobehavioral findings observed in the FOB part of the study. However, REL-related convulsion-like activity, tremor, sternal recumbency, decreased activity, unsteady gait and/or pink to reddish-coloured urine staining and mortality were reported to occur shortly after dosing on study day 1, in 2 out of 15 females (females were included in the 1-month repeat dose tox study but not in the FOB part). These adverse effects were observed at high C_{max} concentrations (C_{max}=6480 µM >100-fold the clinical C_{max}, for the 450 mg/kg dose). The NOAEL was at 150 mg/kg (C_{max}=2090 µM, ~40-fold to the clinical C_{max}).

Imipenem and cilastatin alone and in combination were evaluated in cardiovascular, respiratory, central nervous system and gastrointestinal system pharmacology studies. No cardiovascular or respiratory effects of concern were reported in these studies.

CNS related findings as seizures and convulsion-like activity were observed in the safety pharmacology studies of imipenem in rabbit and rat at approximately 6 -10 times the maximum recommended daily human dose in imipenem/cilastatin/relebactam product (the convulsions reported in a repeat-dose toxicity study in rats conducted after the initial filing for imipenem-cilastatin). Cilastatin alone had no significant actions on the central nervous system.

As also reported in the SmPC of Tienam and proposed imipenem/cilastatin/relebactam SmPC, CNS adverse reactions, such as seizures, confusional states and myoclonic activity, have also been reported in humans treated with imipenem/cilastatin, when recommended dosages of imipenem were exceeded. These reactions have been reported most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Like other β-lactam antibiotics, imipenem seizurogenic potential has been attributed to inhibition of GABA binding to its receptor in the brain, increasing excitability.

Imipenem and cilastatin alone or in combination had no effects of concern in the safety pharmacology evaluating the gastrointestinal system. Unformed stools were noted in the repeat-dose toxicity studies in rats and monkeys. This is a common nonclinical finding in toxicity studies with antibiotics (including imipenem) due to pharmacology mediated changes in the normal intestinal flora.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed where the fixed dose combination IMI/REL was co-administered with any other drug substance. The Applicant based this strategy on the absence of concern in the REL safety pharmacology studies and the previously characterized pharmacology profiles of IMI. Cilastatin, that is designed for coadministration with imipenem, has no antibacterial activity of its own and does not interfere with the activity of imipenem when the 2 agents are combined.

2.3.3. Pharmacokinetics

Methods of analysis

In single-dose PK studies, relebactam (REL) was measured in mice, rats, dogs and monkey plasma using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) detection method following protein precipitation. LC-MS/MS methods, which were validated in accordance with GLP, were also used for determination of REL in the pivotal rat & monkey toxicology and rat & rabbit EFD studies. The lower limit of quantitation (LLOQ) for REL in the GLP plasma assays for mouse, rat, rabbit, and monkey plasma ranged from 10 to 30 ng/mL. The upper limit of quantitation (ULOQ) of the GLP plasma assays ranged from 3,500 to 10,100 ng/mL. The LC-MS/MS assay for rat milk had a LLOQ of 30 ng/mL and a ULOQ of 10,100 ng/mL. A method for determination of cilastatin and imipenem concentrations in monkey plasma was validated with a LLOQ of 99.8 ng/mL and a ULOQ of 39,600 ng/mL.

Absorption

Since REL is intended only for the intravenous route in the clinic, REL has accordingly been non-clinically evaluated only by the intravenous route. After a single IV administration of REL, plasma drug concentration rapidly declined in mouse, rat, dog and monkey. REL overall showed a low plasma clearance (6.2, 12.4, 3.4 and 5.3 ml/min/kg), a small volume of distribution (0.3-0.4 L/kg) and a short half-life (0.9, 0.5, 1.2, and 0.8 hr) in the four preclinical species tested.

REL pharmacokinetics showed linearity after repeated intravenous administration in the toxicokinetic dose range tested in the 3-month intravenous toxicity study in monkeys (25-150 mg/kg). The mean systemic exposure (AUC0-24 hr) and mean Cmax values of REL were approximately dose proportional across the three dose groups on both Study Day 1 and in Study Week 13. Nevertheless, some irregular deviations from linearity were observed in in the other pivotal repeat-dose toxicity studies, as described in the preclinical toxicology section. In addition, after repeat dosing, some decrease in systemic exposure was seen in the 1- or 3-month IV toxicity monkey studies. A 1.3- to 1.6-fold higher REL plasma exposure (AUC) was observed Study day 1 as compared to the corresponding exposure values in Study week 4 or week 13, respectively (for details, see the TK in the preclinical toxicology section).

Since imipenem and cilastatin, as relebactam, are administered IV in the clinic, discussions of the pharmacokinetic properties of the two compounds were limited to IV PK only. Imipenem exhibited a low-to-moderate plasma clearance (ranging from 6.23 mL/min/kg in dogs to 33.0 mL/min/kg in rabbits), and a short half-life (<1 hr) in nonclinical species. The pharmacokinetic profile of cilastatin indicated a half-life almost identical to that of imipenem, supporting the co-administration.

Distribution

The tissue distribution of REL was assessed in male albino (non-pigmented) Wistar- Hannover (WH) rats and pigmented Long-Evans (LE) rats by quantitative whole-body autoradiography (QWBA). Following a 30-min IV

infusion of [14C]REL (28 mg/kg, ~100μCi/kg), radioactivity was rapidly and widely distributed, with most tissues in male WH rats reaching maximum concentrations (Cmax) at 0.5 hr post-infusion (the first sample collection time point). Tissues with the highest concentrations of radioactivity at Tmax were kidney cortex, kidney medulla, urinary bladder, oesophagus, blood, non-pigmented skin, aorta, oral mucosa, lung, and eye uveal tract, ranging from 29 to 315 μg equiv/g. The highest overall concentration of radioactivity was found in the urinary bladder contents (~932 μg equiv/g at 0.5 hr), consistent with renal excretion being the major elimination route. Brain, seminal vesicles, eye lens and bone were among the tissues with lowest concentrations of radioactivity (<1.5 μg equiv/g at Tmax). The low levels of radioactivity in the brain suggests REL is not prone to pass the blood brain barrier. The tissue concentration versus time profiles showed that radioactivity in tissues declined rapidly, consistent with the short half-life of the compound. A similar tissue distribution pattern between albino WH rats and pigmented LE rats indicated that [14C]REL-derived radioactivity did not bind to melanin.

[3H]REL displayed a low binding (~78-90% mean unbound) to mouse, rat, monkey, and human plasma proteins. Plasma protein binding was independent of REL concentration at 5 and 50 μM in all species. The equilibrium blood-to-plasma concentration ratio was ~0.6 in all tested species (mouse, rat, monkey, and human), indicating that REL does not preferentially distribute into red blood cells.

Placental transfer of REL was investigated in pregnant Sprague-Dawley rats and New Zealand White rabbits, following daily IV administration of REL at 450 mg/kg/day in rats on GD 6 through 20 and in rabbits on GD 7 through 20. The ratios of foetal to maternal plasma concentration were ~0.05 in rats and ~0.03 to 0.06 in rabbits. The results suggest that REL has the ability to cross the placenta in both species, with the foetal plasma levels representing ~3-6% of the maternal plasma levels.

The binding of imipenem and cilastatin to human serum proteins is low (~20% and ~40%, respectively). In rats following intravenous administration of radiolabelled imipenem, radioactivity was distributed primarily in the kidney, consistent with renal excretion being the elimination route. The disappearance of radioactivity in tissues parallels the disappearance profile from plasma. Tissue distribution of cilastatin in rats revealed no accumulation of radioactivity in any of the tissues, and the concentration of radioactivity in tissues appears to decrease in parallel with the disappearance profile of plasma radioactivity.

Metabolism

The *in vitro* stability of [3H]REL (10 μM) was evaluated in phosphate buffered saline (PBS, pH 7.2) and in mouse, rat, monkey, and human plasma at 37°C over 4 hr. Data indicated <10% turnover in PBS and plasma. The metabolic turnover of [3H]REL (10 μM) was negligible in rat, monkey, and human hepatocyte suspensions following incubation at 37°C for 2 hr. Overall, minimal metabolism was observed for [3H]REL *in vitro*.

The *in vivo* metabolism of REL was studied in male WH rats following IV administration of unlabelled REL at 4 mg/kg. Two metabolites were identified by LC-MS in rat urine: M1, derived from cyclic urea hydrolysis with loss of CO2, and M2, derived from the reaction of ammonia with the cyclic urea moiety. The structures of M1 and M2 were confirmed by comparing to synthetic standards based on the retention time and MS/MS fragmentations. The levels of REL and these two metabolites in urine were quantified by LC-MS/MS. About 71.2% of the dose was recovered in the urine over 48 hr, consisting of 62.1% REL, 4.9% M1, and 4.1% M2, indicating that REL was cleared primarily via renal excretion of the intact parent in rats, with a small contribution by metabolism. Faecal samples were not collected in the study.

In a follow-up study with radiolabelled [14C] REL (20 mg/kg) administrated intravenously to male WH rats, [14C]REL was detected as the predominant component in urine and faeces (81 and 7.0% of the dose,

respectively), with M1 accounting for ~1.1% and ~0.3% of the administered dose in urine and faeces, respectively. M2 was not detected in the excreta through radiometric or LC-MS analysis. Thus, metabolism appears to be a minor clearance route for REL in rats.

Metabolism of imipenem was shown to occur primarily in the kidney. The major pathway of metabolism of imipenem is by hydrolysis of the beta-lactam ring by the enzyme known as dehydropeptidase-I localized on the brush-border of proximal renal tubular epithelium. The renal metabolic degradation results in a low urinary recovery of intact imipenem in nonclinical species and in humans.

Cilastatin is a dehydropeptidase-I inhibitor that was developed to prevent the renal metabolism of imipenem. Cilastatin, when co-administered with imipenem, increased the urinary recovery of imipenem (from 38% to 67% of the dose in rats, 13% to 76% in chimpanzee, 15-20% to 70% in humans), thereby increasing the antibacterial concentrations in urine and enhancing the therapeutic potential of imipenem for the treatment of urinary tract infections.

Cilastatin undergoes metabolism in nonclinical species and humans to various extent, ranging from 85% in rabbits to <25% in humans. In humans, approximately 10% of the cilastatin administered is found as the N-acetyl metabolite, which has inhibitory activity against dehydropeptidase-I comparable to that of the parent drug

Excretion

The excretion of REL was evaluated in rat and man. Renal excretion was found to be the dominating elimination route, while elimination in faeces was low. Following IV administration of unlabelled 4 mg/kg REL to intact male WH rats, approximately 71% of the dose was accounted for by REL and its metabolites in urine. Following IV administration of radioactive [14C]REL to male WH rats, a total recovery of 94.9% was achieved over 72 hr post-dose, with 84.7% in urine, 7.8% in faeces, and 2.4% in cage wash. The rat unbound renal clearance of REL (12 mL/min/kg) was comparable to the glomerular filtration rate (10-12 mL/min/kg).

In humans, renal excretion of the intact parent is the major route of elimination for REL. The observed renal clearance for REL (250 mg) is ~135 mL/min, close to the plasma clearance (148 mL/min), indicating nearly complete elimination of REL by the renal route. The unbound renal clearance is 173 mL/min (based on an unbound fraction of 0.78) and is greater than the glomerular filtration rate (120 mL/min), suggesting that active tubular secretion is involved in the renal elimination of REL in addition to glomerular filtration, and accounts for ~30% of the total clearance.

Lactational transfer of REL was investigated in pregnant Sprague-Dawley rats by measuring concentrations of REL in maternal plasma and milk on Lactation Day (LD) 14, following daily IV administration of REL at 450 mg/kg/day on GD 6 through LD 14. Maternal plasma and milk samples were collected at 0.25 hr post-dose in rats on LD 14. The ratio of milk to maternal plasma concentration in rats was ~0.05 at 0.25 hr post-dose, indicating excretion of circulating REL into the milk of lactating rats.

Following administration of radiolabelled imipenem to rats, rabbits, monkeys, and humans, >90% of the dose was recovered in urine as intact drug and metabolites. Elimination of imipenem occurs primarily by glomerular filtration and tubular secretion, followed by the dehydropeptidase-mediated metabolism at the brush border of renal tubular epithelium.

Cilastatin is cleared almost solely via renal excretion as intact drug and metabolites in rabbits, monkeys, and humans. The amount of intact cilastatin excreted into urine was ~15% in rabbits, ~45% in monkeys and

~77% in humans. In humans, the renal clearance of cilastatin exceeds the clearance due to glomerular filtration alone, indicating the involvement of active secretion.

2.3.4. Toxicology

The toxicological profile of relebactam (REL) has been evaluated in non-clinical studies in agreement with relevant guidelines. The program includes repeat-dose studies up to 3 months exposure in rats and monkeys, and a repeat dose combination study with REL and imipenem/relebactam. A number of process intermediates/impurities have also been studied. Overall, the toxicity profile of REL has been characterized via single dose toxicity, repeat dose toxicity, genotoxicity, reproductive and developmental toxicity, juvenile toxicity, local tolerance and immunotoxicity studies.

Relevance of animal models

The Wistar Han rat and cynomolgus monkey were selected as the main rodent and non-rodent species in the general toxicity studies. The embryo foetal development studies were conducted in the CD1 mouse, Sprague Dawley rat, and New Zealand White rabbit.

The selection was based on the *in vitro* and *in vivo* metabolic profiles and the demonstration of satisfactory pharmacokinetics in these species. The monkey had previously been used as the non-rodent species for the assessment of toxicological profile of imipenem/cilastatin including the evaluation of renal toxicity caused by imipenem. With respect to the 3Rs principles the selection of the monkey should have been further justified. However, the animal models are considered relevant.

The intravenous (IV) route of administration was utilized in all toxicology studies (except in the first phase of the juvenile study in rat and the EFD study in mouse) to match the intended clinical administration route. The animals were administered once daily, whereas in the clinic, the patients will be administered every 6th hour.

Overall, the animal models are considered relevant.

Single dose toxicity

Single intravenous dose of the assumed maximum feasible dose in rats (up to 450 mg/kg) and monkeys (225 mg/kg) was well tolerated with no test article-related antemortem findings.

Repeat dose toxicity

Relebactam was evaluated in repeat-dose toxicity studies in rats (4 weeks with 4 weeks recovery, and 12 weeks with no recovery phase) and in monkeys (4 weeks with 4 weeks recovery, and 12 weeks with no recovery phase). Relebactam in combination with imipenem and cilastatin was evaluated in a repeat-dose toxicity study in monkey (4 weeks with no recovery phase).

Morbidity and mortality

In the 1-month pivotal repeat dose toxicity studies in rat the 2 female rats in the high dose group (450 mg/kg/day) were found dead shortly after the dose on study day 1. The animals were observed with convulsion like activity, tremors, and sternal recumbency. Reddish-coloured urine was observed in one of the rats. In the following 3-months study, the same maximum dose (450 mg/kg) was selected, and also in this study, 2 female animals died shortly after initiation of administrations. Clinical signs that were observed were

reduced activity, sternal recumbency, convulsion-like activity, rapid breathing and red discolouration in ears. There were no histomorphological findings and the cause of death was not established. In the 1-month study no adverse reactions were observed in the remaining animals, including male rats investigated for CNS safety effects. In the 3-months study, the remaining animals in the high dose group presented with clinical signs such as red discolouration in ears, unsteady gait, reduced activity, and sternal recumbency. It was decided to reduce the maximum dose to 300 mg/kg/day, which was administered Study Day 2 and 3, where after the administration was discontinued for Study Day 4 and 5. Administration resumed on Study Day 6, at which the findings had resolved.

The same maximum dose, 450 mg/kg/day, was used in rats in the reproductive and developmental toxicity studies. In these studies, neither morbidity nor mortality was seen, and additionally no clinical signs were observed. In the repeat dose toxicity studies Wistar Han rats were used, whereas Sprague Dawley rats were used in the reproductive toxicity studies. Wistar Han rats were administered 450 mg/kg/day in a non-pivotal 7 days toxicity study with no observed morbidity or clinical signs. In early exploratory studies with amorphous material of low purity, administration of relebactam 450 mg/kg was associated with acute toxicity and mortality in both Wistar Han and Sprague Dawley rats. In these studies, also the infusion rate was explored, but a lower infusion rate did not reduce the mortality. The measured Cmax in the rats administered 450 mg/kg/day for a month was approximately 6400 µM, which is 130 times the maximum concentration measured in patients (49 µM).

Acute toxicity was also observed in one male monkey administered 225 mg/kg/day. The animal was observed with scant to no faeces, emesis, inappetence, decreased activity, hunched posture, intermittent whole body trembling, and weight loss. The individual was supplemented with food and hydrated, and the physical signs were resolved by day 6. The measured Cmax in the group of animals was approximately 3500 µM, which is approximately 70 times the maximum concentration measured in patients (49 µM). The individual animal in which the observations were made had a three times higher exposure than the other animals in the group. The same dose with amorphous low purity material in an exploratory study, induced transient intermittent unsteady gait, trembling, hunched posture, decreased activity, and lateral recumbency.

Organ toxicity – Kidney

The kidney was identified as a target organ for toxicity of relebactam in both rat and monkey.

In rats, minimal to mild cytoplasmic granularity in the renal tubular epithelium was observed in all animals exposed to daily doses of relebactam for 3 months (65, 150, and 300 mg/kg/day). No evidence of necrotic or degenerative changes was observed. It is not possible to conclude anything about the reversibility of these changes since there was no dose free recovery period included in the study. There were no alterations in other renal-related parameters in the rat studies. Regarding the No Observed Adverse Effect Level, the minimal to mild cytoplasmic granularity was considered non-adverse.

In the 1-month repeat dose toxicity study in monkeys, the highest dose of relebactam, 225 mg/kg/day, induced an increase in kidney weight by 36% (actual weight and related to body and brain weight). In 2 of 6 animals very slight tubule epithelium degeneration was observed and very slight to slight granular cytoplasm in the tubule epithelium in all animals in the group. One female individual in the group also had increased urea nitrogen and creatinine as well as fine granular casts and hyaline casts in the urine. The granular cytoplasm in the tubule epithelium was also observed in one animal administered 75 mg/kg/day. No kidney-related observations were made after the 4 weeks of dose free period. In the three months study, the animals were administered 150 mg/kg/day at a maximum. A dose level at which minimal to mild cytoplasmic

granularity in the tubular epithelium was observed. No epithelial degeneration or effects on clinical pathology were identified.

In the 1-month study in monkeys the effect of relebactam was further assessed by means of biomarkers in urine and electron microscopy. Urine samples from control and high dose animals (225 mg/kg/day) was collected at 3 days, 3 weeks, 1 month, and after the recovery period. The samples were analysed for albumin, N-acetyl-β-D-glucoseaminidase (NAG), kidney injury molecule-1 (KIM-1), total urinary protein, clusterin, and cystatin C. Significant urinary biomarker increases were noted in high dose animals for albumin and total protein, clusterin, and cystatin C, primarily on Study Day 3. KIM-1 levels were significantly increased in study week 5, or study weeks 3 and 5, for seven of ten monkeys at 225 mg/kg/day. All of the recovery animals had normal KIM-1 levels at study week 9. There were no KIM-1 increases on study day 3 in high dose animals. KIM-1 findings correlated with tubular degeneration in 2/2 F. Kidneys from 2 monkeys/group in control and 225 mg/kg/day were evaluated by transmission electron microscopy. In the kidneys from the animals exposed to relebactam, an increased number and size of lysosomes containing electron dense material and concentric lamellar membranous whorls.

In the 1-month toxicity study in monkey where relebactam was administered in combination with imipenem and cilastatin, no histomorphological changes in the kidney was observed. However, the kidney weight (relative to brain weight) had increased with 18%. It was noted that the urine from the treated animals was brown and contained crystals and a slight increase in protein concentration. The relebactam dose in this study was 37.5 mg/kg/day, and 150 mg/kg/day of the combination imipenem/cilastatin (1:1), that is, the intended dose relationship.

In the reproductive toxicity study in rabbit a dose-dependent increase in incidence of rabbits with discoloured urine (orange) was observed at all dose levels. It was argued that the discoloured urine was due to excretion of the open lactam ring of a hydrolysis product of relebactam. This was considered likely but it is not known if this could also explain the observation of brown urine in the combination toxicity study.

Injection site

Irritation of the injection site was noted by clinical observations and histomorphological changes in both rat and monkey and in all groups, including vehicle treated animals.

Imipenem/cilastatin

Animal studies showed that the toxicity produced by imipenem, as a single entity, was limited to the kidney. Co-administration of cilastatin with imipenem in a 1:1 ratio prevented the nephrotoxic effects of imipenem in rabbits and monkeys. Available evidence suggests that cilastatin prevents the nephrotoxicity by preventing entry of imipenem into the tubular cells.

Genotoxicity and carcinogenicity

The genotoxic potential of relebactam was characterized by the Ames test, a chromosome aberration test in CHO-cells, and an in-vivo rat bone marrow erythrocyte micronucleus test. The outcome of the studies was negative, thus, there were no indication that relebactam is genotoxic. In the absence of genotoxicity, and as the proposed treatment duration is relatively short, no carcinogenicity tests have been conducted.

Imipenem and cilastatin (alone and in combinations) were negative in standard battery of *in vitro* and *in vivo* genetic toxicity studies, including V79 mammalian cell mutagenesis assay, Ames test, unscheduled DNA

synthesis assay and in vivo mouse cytogenetics test. No carcinogenicity studies were conducted with imipenem/cilastatin.

Reproduction Toxicity

Studies were conducted to evaluate the standard reproductive and developmental toxicity profile of relebactam: two segment I 'fertility' studies (Sprague-Daley (SD) rats), three piovtal segment II 'EFD' studies (mouse, rat, and rabbit), and one segment III 'prenatal/postnatal' study (SD rats). Additionally, one pivotal juvenile toxicity studies was conducted in SD rats.

Male and female fertility

In the fertility studies in males and females, there were no relebactam-related effects on mating, fertility, or male reproductive assessments (sperm analysis). In the male animals a transient decrease in body weight gain was observed during study week 1 and 3, this did not affect the fertility parameters in the animals. The NOAEL for male and female fertility is therefore ≥450 mg/kg/day, corresponding to an exposure margin of at least 8 times the human exposure based on AUC. In addition, there were no gross or microscopic changes in reproductive organs observed in repeat-dose studies in rats and monkeys for up to 12 weeks of duration.

Embryo-foetal development

Three GLP embryo-foetal development studies were conducted in mice, rats and rabbits. Before these studies were conducted preliminary non-GLP dose finding studies were performed. Relebactam was generally well tolerated across studies.

Mice

The embryo-foetal development in mice was conducted at 0, 80, 200, and 450 mg/kg/day administered subcutaneously. No treatment-related adverse effects were detected in the mothers. In the foetuses there was an apparent increase of skeletal malformations (1, 4, 3, and 5 foetuses in the control, 80, 200, and 450 mg/kg/day group). The Applicant states that the observed skeletal alterations in the pivotal mouse study were within the range of historical control incidences.

The highest dose tested (450 mg/kg/day), rendered a systemic exposure marginal between human and pregnant mice of 6.7x (based on AUC_{0-24}) and x31 (based on C_{max}).

Rat

The embryo-foetal development in rat was conducted at 0, 50, 150, and 450 mg/kg/day. No treatment-related adverse effects were detected in the mothers or the offspring.

The systemic exposure marginal between human and pregnant rat administered the highest dose 450 mg/kg/day was 8.4x (based on AUC_{0-24}) and x111 (based on C_{max}).

Rabbit

The embryo-foetal development in rabbit was conducted at 0, 35, 275, and 450 mg/kg/day.

No treatment-related adverse effects were detected in the mothers except for an observation on discoloured urine which is thought to be due to excretion of a hydrolysis product of relebactam.

A slight increase in the incidence of foetuses with either a malformation or variation of the hyoid bone was observed (M/V: 1/1, 0/2, 0/2, and 3/5 foetuses in the control, 35, 275, and 450 mg/kg/day group). The

Applicant considers this unrelated to relebactam due to the isolated event and since no other relebactam related variations were observed.

The systemic exposure marginal between human and pregnant rabbit administered the highest dose 450 mg/kg/day was 29x (based on AUC_{0-24}) and x147 (based on C_{max}).

Prenatal/postnatal study

The potential effects of relebactam on development, growth, behaviour, reproductive performance, and fertility of F1 generation were evaluated in rats after administration of 0, 64, 200, and 450 mg/kg/day to F0 females from gestation day 6 through day 20 postpartum. Furthermore the F1 pups were investigated for cohabitation on post-natal week 12.

Mean plasma exposure of relebactam for F0 females on gestational day 15 for the highest dose (450 mg/kg/day) was 3020 µMxhr which is 9.1x the human exposure at steady state.

The relebactam concentration in milk or exposure in pups was collected from separate studies in rats. The foetal plasma levels were approximately 5% of the maternal plasma levels on gestation day 20 after administration of 450 mg/kg/day on GD7 through 20. In another study the ration of milk to maternal plasma concentration in rats was approximately 0.05 15 min post dose.

Juvenile

One pivotal juvenile toxicity study was conducted in Sprague Dawley rats. Relebactam was administered on postnatal day 14 – 56 with a recovery phase until PND 85. No clinical observations or alterations in developmental landmarks (vaginal opening, preputial separation), clinical pathology, organ weights, gross findings or femur length related to relebactam was observed.

The systemic exposure marginal between adult human and the juvenile rats administered the highest dose 450 mg/kg/day was 6x (based on AUC_{0-24}) and 78x (based on C_{max}).

Imipenem/cilastatin

No treatment-related effects on fertility are noted after imipenem/cilastatin administration to male and female rats.

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40/40 mg/kg/day (bolus intravenous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea, abortion, and death in some cases. When doses of imipenem-cilastatin sodium (approximately 100/100 mg/kg/day or approximately 3 times the maximum recommended daily human dose in imipenem/cilastatin/relebactam product) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups

Toxicokinetic data

Toxicokinetics of relebactam was characterized in all the pivotal toxicity studies. There were no differences between males and females in the TK parameters in either rat or monkey. In the one-month toxicity studies in both rat and monkey where the highest doses were administered, 450 mg/kg/day in rat and 225 mg/kg/day in monkey, a slight change in dose proportionality was observed. The systemic exposures in the

high dose animals were higher than expected. Possibly due to an effect on renal function and lower excretion caused by high exposure of relebactam.

Local Tolerance

Relebactam is classified as a non-irritant.

Impurities

The specification levels suggested by the applicant for the impurities desulfated (NH,OH), t-butyl impurity, Ritter impurity, and open ring hydrolysis degradate (0.50, 0.30, 0.23, and 0.50 wt%) are qualified in the non-clinical pivotal repeat dose toxicity study in rats.

2.3.5. Ecotoxicity/environmental risk assessment

The ERA is based on relebactam which has a molecular weight of 366 g/mole, a water solubility of 63.3 g/L (pH7), and a log K_{OW} < -2 (pH 7). The ERA Phase I surface water predicted environmental concentration (PECSW) was calculated to 5.0 µg/L using the default Fpen (0.01) and the maximum dose of 1000 mg/day. Based on the OECD 308 test, the persistence against aerobic degradation in whole fresh water-sediment systems is between DT_{50} 20-41 days (20 °C) or 43-88 days (12 °C).

The organic content solid adsorption coefficient for relebactam were below 10000 L/kg for sludge and soil (K_{OC} 18-202 L/kg), making it unlikely that there is a terrestrial environmental risk due to agricultural use of sludge. The lowest NOEC for aquatic toxicity was 0.67 mg/L using *Anabaena flos-aquae* while the most sensitive NOEC for sediment-dwellers (*C. riparius*, NOEC 18 mg/kg) was for midge emergence.

Relebactam is not classified as a PBT or vPvB candidate. Based on the Phase I PECSW, the applicant has provided a set risk quotients/ratios that are below 0.1 for sludge microorganisms and below 1 for other compartments.

Summary of main study results

Substance (INN/Invented Name): Relebactam (MK-7655)			
CAS-number (if available): 1174020-13-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{OW} < -2	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	5.0	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	55.9 g/L (pH 5) 63.3 g/L (pH 7) 76.0 g/L (pH 9)	
Adsorption-Desorption	OECD 106	*Soils* *1.* K_{oc} = 26.5 L/kg *2.* K_{oc} = 68.2 L/kg *3.* K_{oc} = 65.2 L/kg *4.* K_{oc} = 202 L/kg	1: Loam 2: Loamy sand 3: Sandy loam 4: Clay

		Sludges *5.* K_{oc} = 61.5 L/kg *6.* K_{oc} = 17.9 L/kg			No trigger of terrestrial studies as <10000L/kg.
Biodegradation in activated sludge	OECD 314B	Biodegradation half-life: 88 Elimination rate constant: 0.0079 day^{-1}			
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Tauton /Weweantic River $DT_{50, water}$ = 17/38 days $DT_{50, sediment}$ = 28/47 days $DT_{50, whole\ system}$ =20/41 days Corrected to 12 °C: $DT_{50, water}$ = 36/81* days $DT_{50, sediment}$ = 60/100 days $DT_{50, whole\ system}$ =43/88 days % shifting to sediment >10%			*Relebactam is vP in fresh water.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	12	mg/L	*Pseudo-kirchneriella subcapitata*
			11 (0.67)	mg/L	*Anabaena flos-aquae*
Daphnia sp. Reproduction Test	OECD 211	$NOEC_{Survival}$ $NOEC_{fecundity}$	9.6 2.7	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	9.2	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10} (NOEC) EC_{50}	96.3 >1000	mg/L	
Phase IIb Studies					
Chronic toxicity to sediment dwelling organism	OECD 218	$NOEC_{emergence}$ $NOEC_{dev\ rate}$	18 31	mg/kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

Pharmacology

For assessment of primary pharmacodynamics, see clinical section on pharmacodynamics.

Based on the lack of any findings in the safety pharmacology or toxicity studies adequate for the intended therapeutic concentration range, the off-target screen appears to have been sufficient and CHMP agreed that can be considered acceptable.

Overall for relebactam, no safety pharmacological findings in a clinically relevant dose range were observed. Due to the high exposure marginal (Cmax at >100-fold the clinical Cmax), for the acute toxicity findings in the 1-month repeat-dose IV study in rats, occurring in conjunction with the neurobehavioural FOB study, the applicant considered these to be of limited clinical relevance. This conclusion is agreed on.

For imipenem and cilastatin alone and in combination, no cardiovascular, respiratory or gastrointestinal effects of concern were reported. However, CNS related findings, as seizures and convulsion-like activity, were observed at approximately 6 -10 times the corresponding maximum recommended daily human dose of Recarbrio. As reported in the Tienam SmPC and proposed Recarbrio SmPC, CNS adverse reactions, such as seizures, confusional states and myoclonic activity, have also been reported in humans treated with imipenem/cilastatin when recommended dosages of imipenem were exceeded. For further discussion of the acute CNS-related toxicity effects, see the non-clinical toxicological section. Cilastatin alone had no significant actions on the central nervous system.

For relebactam it was noted only males were used in the CV and CNS GLP-studies. However, since no substantial gender differences were observed in the repeat dose toxicology studies, this is considered acceptable. It was also noted Mongrel dogs were used in the CV study in anesthetized dogs, which presents problems with regard to animal to animal variability by introducing wider genetic differences which potentially affects the PK and/or PD results. In order to best investigate the cardiovascular effects of REL, the Applicant could have used a pure breed of dogs such as beagles. However, since this study was not pivotal and CV effects were studied in humans in thorough QTc study, this is not considered critical.

In conclusion, the non-clinical data package, considering secondary and safety pharmacology raise no objections for the use of Recarbrio in the intended disease indications.

It should be noted that the assessment of the non-clinical primary pharmacodynamics (*in vitro* and *in vivo*) is carried out in the clinical section.

Pharmacokinetics

For relebactam, no single-dose PK data was provided for rabbit used for the EFD studies. However, a dose-finding in male and female rabbits is carried out for the EFD studies. Furthermore, the bioanalytical method report for the plasma exposure measured in the placental transfer study was GLP validated. Overall this is considered sufficient by CHMP.

The Applicant states, the half-life of REL in humans is similar to that of IPM and CIL and also suggest the REL half-life provides support for the suggested dosing interval of q6h. Upon CHMP request during the assessment, the Applicant has also provided the half-life of IPM and CIL, which is considered supportive for the co-administration.

It is noted that no studies on *in vivo* metabolism of REL have been carried out in rabbit or monkey that were used in reproductive toxicity or CV and repeat dose toxicity studies, respectively. However, since no major REL metabolites have been identified in humans, this is considered acceptable by CHMP.

For imipenem and cilastatin, distribution and elimination studies were consistent with renal excretion being the main elimination route for parent and metabolites. Moreover, the metabolism of imipenem occurs primarily in the kidney mainly by hydrolysis of the beta-lactam ring by the enzyme known as dehydropeptidase-I resulting in a low urinary recovery of intact imipenem. However, since cilastatin is a dehydropeptidase-I inhibitor that according to the Applicant was developed to prevent the renal metabolism of imipenem, cilastatin increased the urinary recovery of imipenem. Thereby the antibacterial concentrations in urine was increased and the therapeutic potential of imipenem for the treatment of urinary tract infections was enhanced. The submitted documentation seems to support this approach.

During the assessment the Applicant has submitted a non-clinical summary addressing the pharmacokinetic section regarding imipenem and cilastatin.

Toxicology

In the 1-month pivotal repeat dose toxicity studies in rat the 2 female rats in the high dose group (450 mg/kg/day) were found dead shortly after the dose on study day 1. The animals were observed with convulsion like activity, tremors, and sternal recumbency. In the following 3-months study, the same maximum dose (450 mg/kg) was selected, and also in this study, 2 female animals died shortly after initiation of administrations. It is acknowledged that the exposure margins are large and that the clinical relevance for the observed acute toxicity could be limited. However, since the observed effects are indicative of CNS effects and adverse CNS reactions, such as myoclonic activity, confusional states, and seizures have been reported in patients for imipenem/cilastatin, the Applicant was asked during the assessment to elaborate on this acute toxicity and its possible clinical relevance. The Applicant provided a discussion and CHMP agreed that the observed clinical signs in rats occurred at clinically irrelevant concentrations, and that the clinical signs were only observed in the rat and not in the monkeys. Furthermore, the relebactam in the imipenem/cilastatin/relebactam combination did not render an increased number of CNS adverse reactions compared to imipenem/cilastatin. The clinical risk of seizure and other CNS adverse reactions is presented in the SmPC section 4.4 Special warnings and precautions for use and is thus adequately addressed.

The kidney was identified as a target organ for toxicity of relebactam in both rat and monkey. The Applicant describes the observed epithelial granulation as indicative of an adaptive process allowing compound disposition via lysosomes. This argument is further supported by the results from the electron microscopic evaluation in which increase of the number and size of lysosomes were noted. In the current SmPC of Tienam it is suggested that cilastatin prevents the imipenem induced nephrotoxicity by preventing entry of imipenem into the tubular cells. In light of the main excretory pathway (renal) together with the described findings, and the previous established toxicological profile of imipenem, the Applicant was asked by CHMP during the assessment to further discuss possible cause of the observed renal toxicities, if a possible synergistic effect of imipenem and relebactam on the tubular cells exist, if cilastatin can protect against nephrotoxicity caused by relebactam, and clinical possible implications on patients and especially patients with reduced renal function. It is not clear if the same pathway is involved for the nephrotoxicity induced by relebactam and imipenem. The transport of relebactam, and possibly imipenem, into the kidney tubular cells involves the OAT3 transporter. The applicant discussed the theoretical possibility that cilastatin as an inhibitor of OAT3 could block the entrance of relebactam (and possibly imipenem) via OAT3 into the renal tubular epithelium and thereby preventing its nephrotoxicity. However, it is not known if the plasma levels of cilastatin are high enough to sufficiently block the transporter of both imipenem and relebactam in order to avoid nephrotoxicity.

Relebactam alone induced granularity in the cytoplasm of proximal tubular epithelial cells in rats at clinically relevant exposures and at double the exposure in monkeys. These findings were considered non-adverse. No synergistic toxic effects were observed when relebactam was co-administered with imipenem and cilastatin in monkeys. In this study, however, the relebactam dose was lower (37.5 mg/kg/day) than in the single component study, rendering an exposure only 1.3x the AUC observed in patients. However, the results from the completed clinical trials are not indicative of an increased risk of renal toxicities when imipenem is administered with cilastatin only or when relebactam is added. In patients with impaired renal function, it is recommended to reduce the dose both with imipenem/cilastatin and imipenem/cilastatin/relebactam; this is included in the Recarbrio PI.

The Applicant’s position is that no additional specific urinary biomarkers to monitor kidney toxicity is necessary. This is accepted by CHMP, since the dose levels in patients with an impaired renal function is adjusted based on creatine clearance.

Reproductive and developmental toxicity

In the embryo-foetal development in mice there was an apparent increase of skeletal malformations (1, 4, 3, and 5 foetuses in the control, 80, 200, and 450 mg/kg/day group). The Applicant states that the observed skeletal alterations in the pivotal mouse study were within the range of historical control incidences. The historical data was provided in response to the questions in the first round of the procedure. The data was based on 1189 foetuses in 102 litters for all observations except skull bone malformation (640 foetuses evaluated in 102 litters). The data was collected from only 5 control groups. The data was obtained 2005-2010 and the study conducted during 2012. It is not clear how the data was calculated.

During the procedure, the Applicant provided additional discussions regarding the findings. The incidence of skeletal malformations in the pivotal EFD study in mice was slightly higher than previously observed incidences. The skeletal malformations in mice consisted of cleft palate and skull malformation, cervical and lumbar vertebra malformation, and absent and extra vertebra. Regarding the cleft palate malformation, the finding consisted of the subcategories split palatine and split axis. Split palatine represents the skeletal confirmation of the external finding of cleft palate. The number of observations of cleft palate was within the historical control range. Only one individual (low-dose group) was observed with the split axis. Regarding the other observed malformations, it is somewhat unclear, but considering the low number of observations and the fact that the findings are not observed in rats or rabbits, CHMP agreed that the findings in mice could be considered unrelated to the treatment with relebactam.

A slight increase in the incidence of foetuses with either a malformation or variation of the hyoid bone was observed in the embryo-foetal development study in rabbit. The historical control incidences on hyoid bone malformation and variation in rabbit was submitted in response to questions in the first round of the procedure. The data was based on 1465 foetuses in 172 litters collected 2008-2012. The study was conducted in 2015. It is not clear how the data was calculated. The incidence of hyoid bone malformation was within the historical control range, while the incidence of variations was above the historical range. It was not possible to exclude a potential test article-related effect. In response, the Applicant clarified that the difference between malformation and variation in the rabbit EFD study was the severity of the findings since the observations consisted of misshapen or bent thyrohyoid. It is thus reasonable to combine the incidence of hyoid bone malformations and variations. This is agreed. The Applicant also presented historical control ranges for the combined incidence of malformations and variations from another site. While historical control data from other sites could be questionable the actual numbers were convincing that the numbers of combined malformation and variation in the rabbit were well within the historical control range.

In the prenatal/postnatal study in rats, there were a number of dead pups in the PPND study, rendering a slightly reduced percentage of live pups delivered (100 % in control and 91-92% in the 200 and 450 mg/kg/day groups). In the Applicant's responses during the assessment it was clarified that no examinations were performed on pups that died before litter processing in the rat PPND study. This was according to study protocol and standard operating procedures. The Applicant claimed that the lower percentages of live pups at the 200 and 450 mg/kg/day groups was not related to relebactam based on lack of dose response based on plasma AUC and historical controls.

In the initially proposed Recarbrio SmPC section 5.3, the wording regarding imipenem/cilastatin and pregnancy in cynomolgus monkeys included a comparison with the human dose based on body surface area. The Applicant was asked to provide a clarification on how the data had been calculated. The presented data were not fully acceptable, since different human body weights were used in the calculations. In the calculation for the Human Equivalent Dose (HED) for the 100 mg/kg/day monkey dose (100/3.1=32.3 mg/kg/day) assumes a human body weight of 60 kg. The recommended human dose (RHD) for 2000 mg/day

is thus 33.3 mg/kg/day. The comparison of the doses is thus 32.3/33.3 = 0.97. It is agreed that the HED conversion could be used, however, for consistency, CHMP agreed to request the Applicant to use the wording from the Tienam PI, previously agreed upon by CHMP.

Impurities

In the submitted documents for the Ritter impurity, different specification limits as well as different impurity levels in the nonclinical studies are presented. During the assessment, the presented figures were clarified, and the dose multiple based on mg/kg was 8.48.

Environmental risk assessment

CHMP noted that the environmental risk assessment was not submitted for imipenem and for cilastatin. Environmental testing is currently underway and CHMP requested that the results of the studies should be submitted for assessment by the end of 2020.

In terms of the water/sediment study (OECD 308) the applicant presented DT50water and DT50sediment normalised to European average temperature of 12 °C as requested in the first round of the procedure. 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).

2.3.7. Conclusion on the non-clinical aspects

CHMP agreed that from a non-clinical point of view, with regard to preclinical secondary & safety pharmacology, pharmacokinetics and toxicology, the application for imipenem/cilastatin/relebactam is approvable.

The CHMP considers the following measures necessary to address the non-clinical issues: The Environmental risk assessment of imipenem and cilastatin needs to be submitted post approval, not later than the end of Q4 2020.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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 Type	Study Number	Title	N
Healthy Subject PK and Initial Tolerability Trials	PN001	A Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Intravenous Single Doses of MK-7655 and Intravenous Single and Multiple Doses of MK 7655 Dosed in Combination with Imipenem/Cilastatin IV	106
	PN007	A Study to Evaluate the Intrapulmonary Pharmacokinetics of Multiple Intravenous Doses of MK-7655 Dosed in Combination with Imipenem/Cilastatin IV in Healthy Subjects	17
Intrinsic Factor PK Trials	PN002	A Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Doses of MK-7655 Dosed in Combination with Imipenem/Cilastatin IV in Healthy Elderly Male, Elderly Female and Young Female Subjects	24
	PN005	A Single-Dose Study to Investigate the Pharmacokinetics of MK-7655 in Subjects With Impaired Renal Function	49
	PN012	A Single- and Multiple-Dose Clinical Trial to Study the Safety, Tolerability and Pharmacokinetics of MK-7655 in Healthy Japanese Subjects	19
Extrinsic Factor PK Trials	PN019	A Randomized, Two-Period, Crossover Study to Examine the Effect of Probenecid on the Pharmacokinetics of Relebactam (MK-7655) Administered as MK 7655A (500 mg Imipenem/500 mg Cilastatin/250 mg Relebactam) in Healthy Adult Subjects	14
Healthy Subject PK-PD Trials	PN009	A Single Dose Study to Assess the Effect of MK-7655 on the QTc Interval in Healthy Adult Subjects	36

Study Type	Study Number	Title	N
Study Reports and Related Information of Controlled Clinical Studies Pertinent to the Claimed Indication	PN003	A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Urinary Tract Infection	302 randomized; 198 treated with IMI + REL
	PN004	A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Intra-Abdominal Infection [cIAI]	351 randomized; 231 treated with IMI + REL
	PN013	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Estimate the Efficacy and Safety of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem/Cilastatin in Subjects with Imipenem-Resistant Bacterial Infection	50 enrolled; 34 treated with IMI/REL

2.4.2. Pharmacokinetics

As relebactam is a new chemical entity, pharmacokinetic data should aim at describing the disposition of the compound in order to possibly support dosing recommendations and predict situations and patients where pharmacokinetics may be different from that in the average clinical study patient. For imipenem and cilastatin, the Applicant provided information which is in line with that presented in the SmPC of the approved product Tienam. For both imipenem and relebactam, the PK data are used in the PK/PD models of importance to support efficacy and safety in the proposed indications.

Bioanalysis methods

All bioanalytical methods for quantification of relebactam, imipenem and cilastatin in clinical samples, were based on liquid chromatography (either HPLC or UPLC) with tandem mass spectrometry (MS/MS).

Population pharmacokinetic analysis

Separate models were constructed for imipenem and relebactam. Cilastatin was not analysed in the studies, and no popPK model was developed. Data were included from seven completed Phase 1 studies with rich PK sampling (PN001, PN002, PN005, PN007, PN009, PN012 and PN019), two completed Phase 2 studies (PN003 and PN004) and one completed double-blinded Phase 3 study (PN013) with sparse sampling. The structural and stochastic models were chosen based on the phase I data; two compartment model of disposition with zero order IV infusion and first order, linear elimination; incorporating BSV in CL, V1 and V2. The tested covariates were Clcrea, weight, healthy/patient, age, sex and race.

The parameter estimates of the final model, including Clcrea and weight as covariates on imipenem clearance and Clcrea on relebactam clearance. Health status as a covariate on relebactam clearance was initially found significant but was not retained in the backward deletion. Weight was included as a covariate on V1 for both entities, whereas health status was included only for imipenem. The final covariate relationships are displayed in Table 8. Renal impairment had a substantial effect on the exposure of both imipenem (1.37, 1.57 and 5.17-fold in mild, moderate and severe RI, respectively) and relebactam (1.54, 2.17, and 3.99-fold). Weight had a minor impact on the exposure of both compounds.

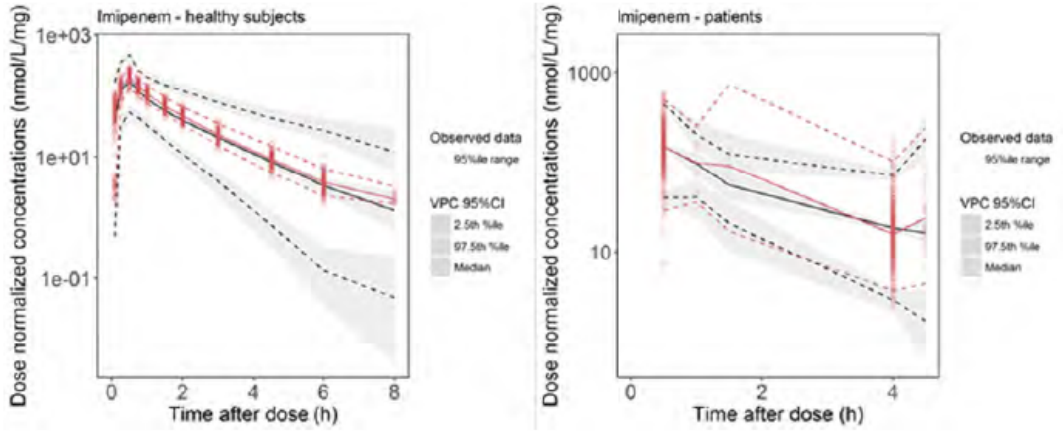
Table 1. Final Imipenem and Relebactam Model Parameter Estimates

	Imipenem				Relebactam			
	NONMEM		Bootstrap[d]		NONMEM		Bootstrap[d]	
Parameter	[a]Estimate (RSE%)	[c] 95% CI	[a] Estimate (RSE%)	[c] 95% CI	[a]Estimate (RSE%)	[c] 95% CI	[a]Estimate (RSE%)	[c] 95% CI
CL (L/h)	12.53 (2.0)	12.04 - 13.02	12.54 (2.0)	12.04 - 13.01	7.02 (2.0)	6.75 - 7.29	7.02 (1.9)	6.74 - 7.27
V1 (L)	15.83 (3.2)	14.82 - 16.83	15.81 (3.6)	14.62 - 16.89	11.08 (2.9)	10.45 - 11.71	11.08 (2.9)	10.48 - 11.72
V2 (L)	5.84 (4.0)	5.39 - 6.29	5.85 (3.9)	5.40 - 6.29	6.41 (3.8)	5.94 - 6.89	6.42 (3.7)	5.93 - 6.88
Q (L/h)	11.09 (6.5)	9.68 - 12.49	11.11 (6.6)	9.73 – 12.57	10.45 (6.8)	9.04 - 11.85	10.43 (6.8)	8.99 - 11.88
Covariates on CL								
CrCL (power)	0.46 (8.1)	0.39 - 0.53	0.46 (8.2)	0.39 - 0.53	0.75 (8.3)	0.62 - 0.87	0.75 (8.6)	0.62 - 0.87
WT (power)	0.33 (30.5)	0.13 - 0.53	0.34 (32.0)	0.12 - 0.55	-	-	-	-
Covariates on V1								
WT (power)	0.74 (19.1)	0.46 - 1.01	0.75 (22.1)	0.42 - 1.07	0.70 (15.8)	0.48 - 0.92	0.70 (17.3)	0.45 - 0.93
HLTH	-0.29 (9.5)	-0.34 - -0.23	-0.28 (10.3)	-0.34 - -0.22	-	-	-	-
Random effects BSV	[e]CV% (shrink)	RSE%	[e]CV%	RSE%	[e]CV% (shrink)	RSE%	[e]CV%	RSE%
BSV in CL	51.8 (5.1)	9.3	51.8	9.5	45.0 (16.4)	11.6	45.0	11.6
BSV in V1	74.4 (7.4)	11.6	74.7	12.2	59.5 (18.8)	11.9	59.5	12.3
BSV in V2	35.0 (52.9)	32.7	34.8	33.2	41.1 (49.8)	30.3	41.0	30.7
[d]Corr CL ~ V1	0.77	12.0	0.77	12.9	0.63	14.2	0.63	14.5
Random effects BSV								
Proportional Error	16.1 (19.0)	6.7	16.1	6.9	15.3 (14.1)	5.6	15.3	5.6

[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 $\omega_{ij}^2/\text{sqrt}(\omega_{ii}^2 * \omega_{jj}^2)$
BSV: Between Subject Variability; CI: Confidence Interval; Corr: Correlation coefficient; CV: Coefficient of Variance; RSE: Relative Standard Error; shrink: Shrinkage
Source: Merck-7655A/Analysis/e-model-finalization/run60.lst & Merck-7655A/Analysis/e-model-finalization/run60bs

Dose normalized VPCs for imipenem and relebactam are shown below (Figure 8). Observed as well as model predicted concentrations (nmol/L) were divided by the respective dose (mg) to give dose normalized concentrations (with units of nmol/L/mg) to account for the differences in doses used across the studies.

Figure 4. Visual Predictive Check (dose normalized) for IPM stratified by healthy, patients and renal impairment status.



Solid lines represent median (50th percentile) concentrations values. Dashed lines represent the 5th of 95th percentile values. Red = observed concentrations; Black = model predicted concentrations. Shaded areas represent the 95th confidence interval (CI) around the 5th, median and 95th model predictions.

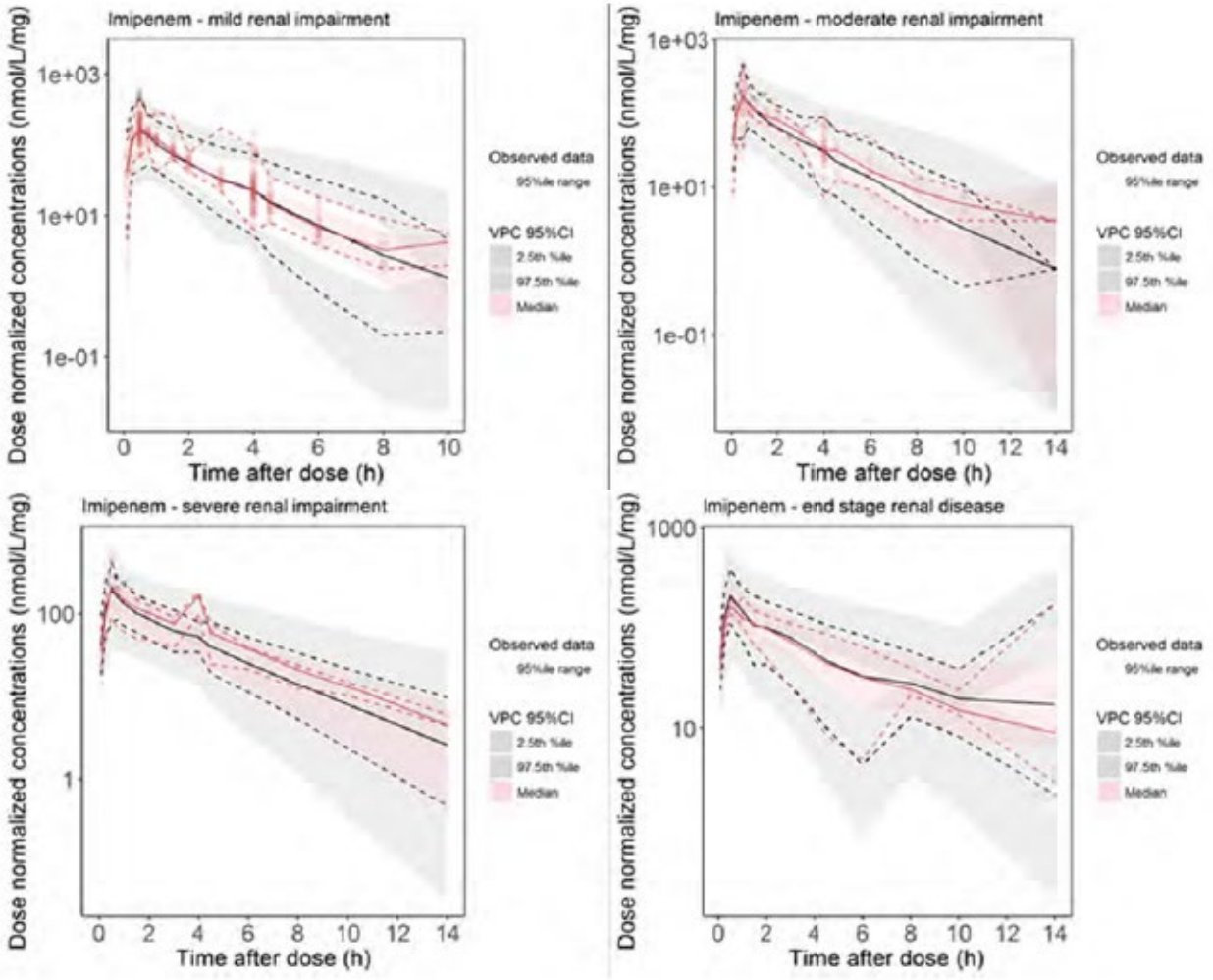
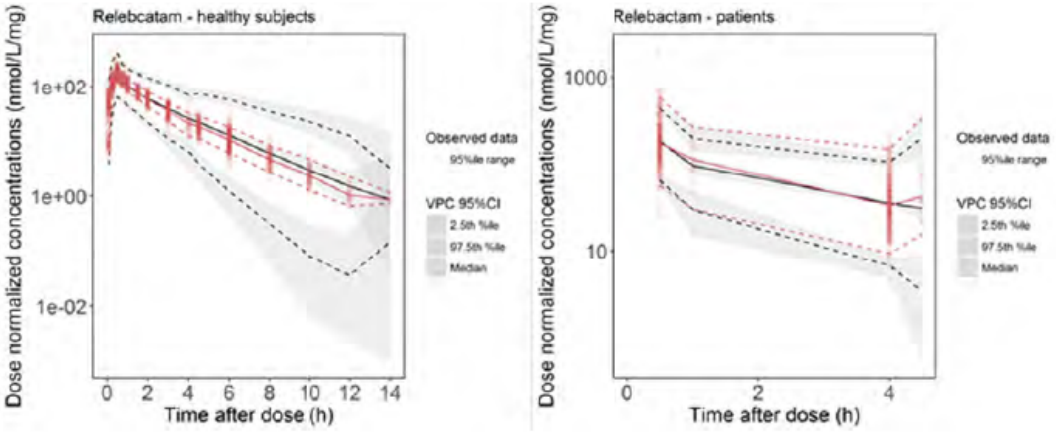
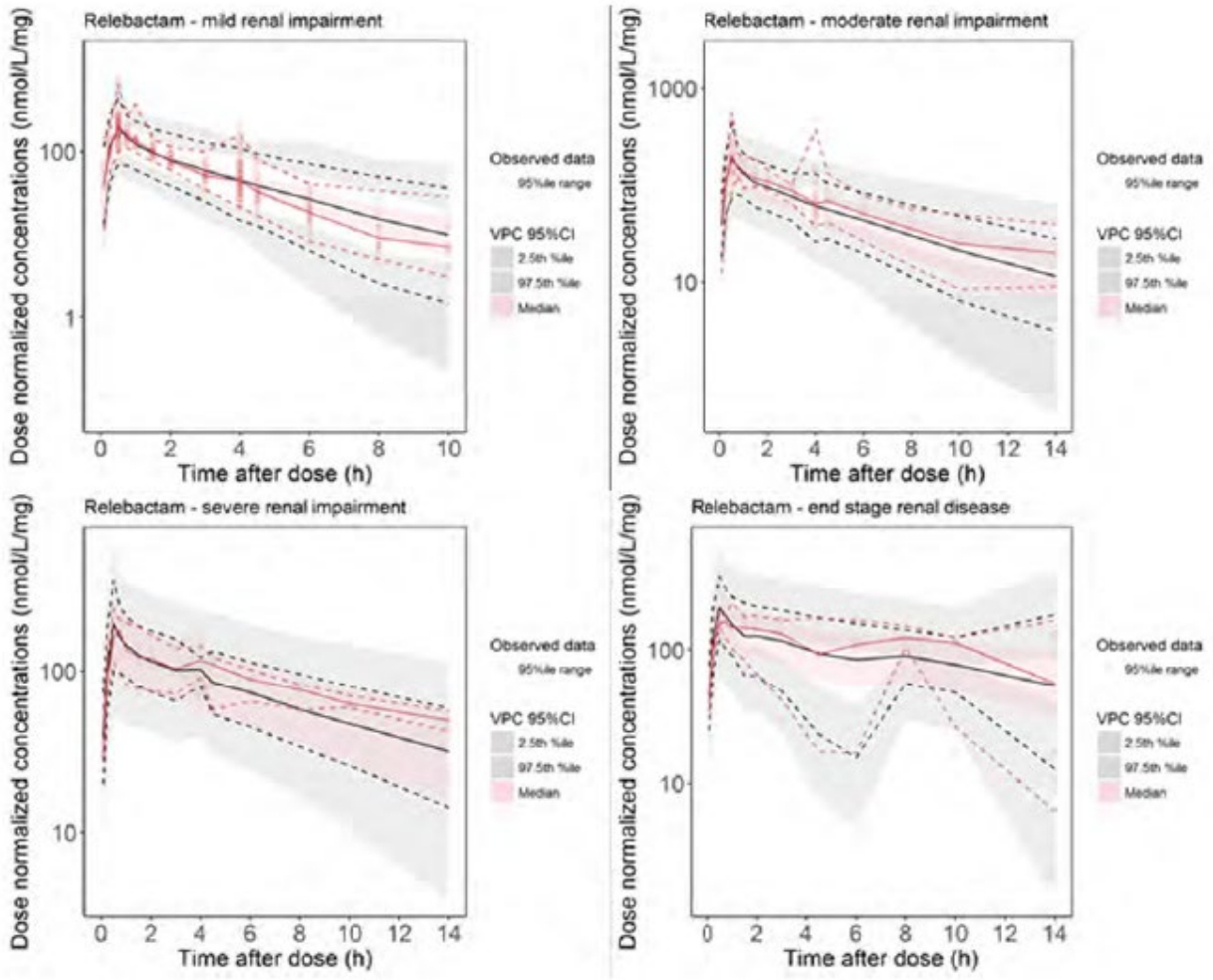

Imipenem - mild renal impairment
Imipenem - moderate renal impairment
Imipenem - severe renal impairment
Imipenem - end stage renal disease
Dose normalized concentrations (nmol/L/mg)
Time after dose (h)
Observed data
95%ile range
VPC 95%CI
2.5th %ile
97.5th %ile
Median

Figure 5. Visual Predictive Check (dose normalized) for REL stratified by healthy, patients and renal impairment status.



Solid lines represent median (50th percentile) concentrations values. Dashed lines represent the 5th of 95th percentile values. Red = observed concentrations; Black = model predicted concentrations. Shaded areas represent the 95th confidence interval (CI) around the 5th, median and 95th model predictions.



Absorption and distribution

All studies are performed with solutions for IV infusion. According to the popPK model, the Vss of relebactam is 19L, and the corresponding value for imipenem is 24 L All three compounds have a modest plasma protein binding, with an unbound fraction of relebactam around 78%. A distribution study to lung (ELF, alveolar cells) was performed in healthy volunteers after administration of multiple doses of imipenem/relebactam. Both relebactam and imipenem were distributed to bronchoalveolar fluid to a similar extent. The exposure in this compartment appeared lower than in plasma, the estimated exposure was around 50% of that in plasma for both compounds. Relebactam was also found in alveolar cells, in similar or lower concentrations than in ELF. Imipenem, however, did not appear to distribute to alveolar cells.

Elimination

In the phase I study P001V01 urine sampling was performed and the excretion of both relebactam, imipenem and cilastatin was assessed. Almost all of a given dose of relebactam was retrieved unchanged in urine. In the single dose groups fe was 95-100% over 24 hours, and in the multiple dose groups fe was 89-100% over a dose interval. Renal clearance was independent of dose and was estimated to 127-182 ml/min in the different dose groups, 135 ml/min at the 250 mg dose.

Imipenem was also found in a high extent unchanged in urine. After a single dose of 500 mg, in combination with cilastatin and with or without co-administration of relebactam, the fraction retrieved unchanged in urine ranged from 53 to 71%, with a renal clearance of 106-139 ml/min. For cilastatin, 71-95% was excreted unchanged and renal clearance was estimated to 173-202 ml/min.

Given that the estimated renal clearance of relebactam (~ 135 ml/min) was higher than what would be the expected passive filtration (fu x GFR ~0.78x120 ml/min = 94 ml/min), a role of active renal secretion (around 30% of total clearance) is expected for relebactam. Therefore, identification of potential active transport proteins in the kidney was performed.

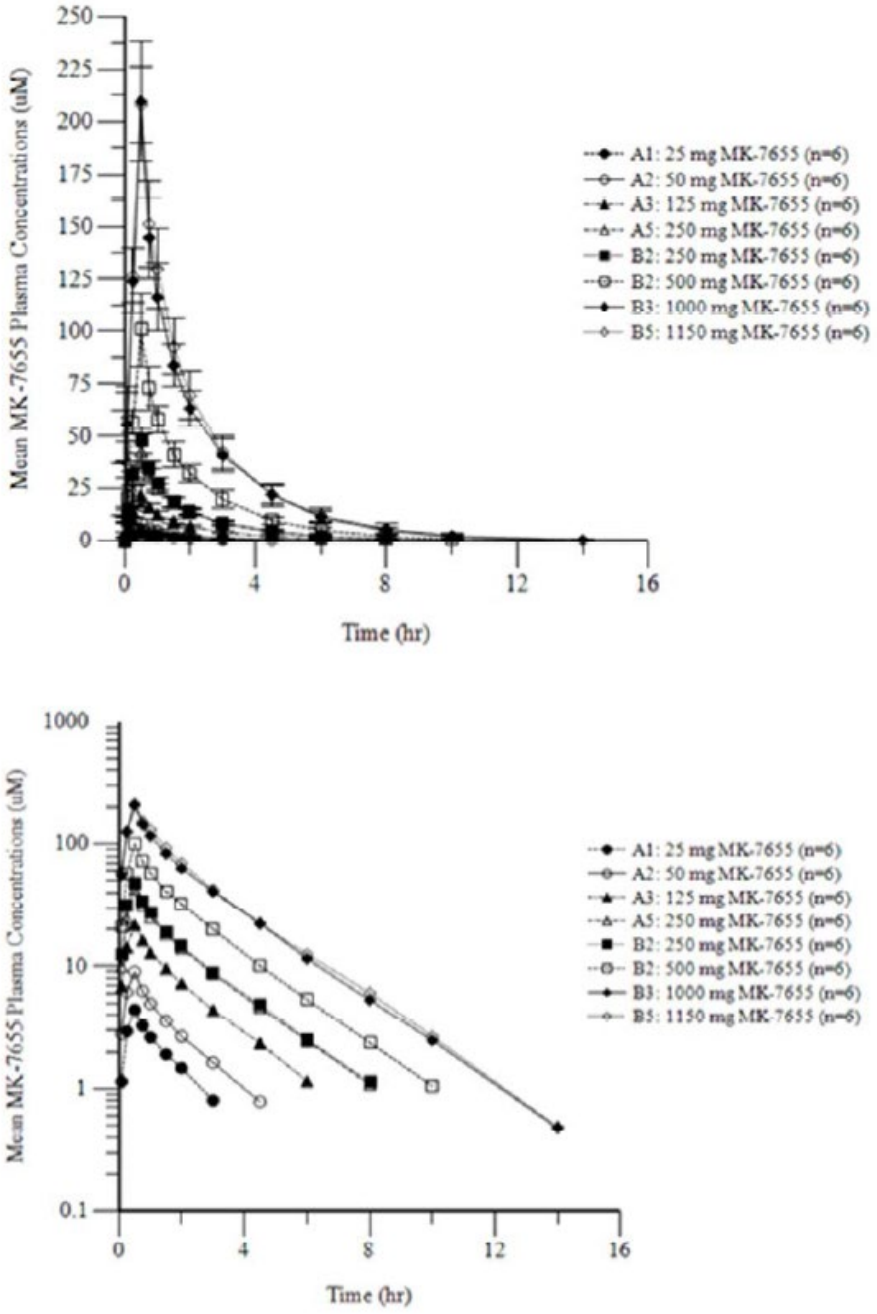
Several *in vitro* systems (cell monolayers, cell suspensions, membrane vesicles) were used in order to investigate transporters which are relevant for disposition of relebactam. Investigated transporters included: P-gp, BCRP, MRP2, MRP4, OAT1, OAT3, OAT4, OCT2, MATE1 and MATE2K. Applicant has concluded that relebactam was a substrate of OAT3, OAT4, MATE1 and MATE2K. The clinical relevance of OAT-transport was investigated further in a DDI-study with probenecid.

Relebactam, as well as cilastatin is almost entirely excreted unchanged in urine and no clinically relevant metabolism occurs. Imipenem is partly metabolised in the kidney by dehydropeptidases, which are inhibited by cilastatin. No indications of metabolism were observed *in vitro* in hepatocytes.

Dose proportionality and time dependencies

Following single-dose administration as a 30-minute infusion, relebactam plasma concentrations declined biexponentially with a GM terminal t½ ranging from 1.35 to 1.8 hrs over the 25 mg to 1150 mg dose range (Figure 10). Analysis of dose proportionality showed that the slope was very close to 1 (1.01, 95% CI 0.99-1.03) when a linear mixed effects model was used, including ln-dose as a continuous effect, performed on natural log-transformed values.

Figure 6. Single dose PK profiles of relebactam in study P001.



In the multiple-dose panels, doses between 50 mg and 625 mg were tested, administered every 6 hours. Clearance and half-life were similar to the single dose part, and PK (AUC0-6h as well as C at the end of infusion) appeared linear with dose (Table 9). Minimal accumulation was observed.

Table 2. Summary PK parameters of relebactam multiple dose in study P001.

Summary Plasma Pharmacokinetics of MK-7655								
MK-7655 Dose with PRIMAXIN® IV (500 mg)	Part	Panel	Day	N	AUC0-6hr (uM*hr)†	Ceoi (uM)†	Tmax (hr)‡	Apparent Terminal t1/2 (hr)§
50 mg	II	C	1	6	17.6 ± 1.94	9.84 ± 1.03	0.48(0.48-0.48)	1.64 ± 0.0835
50 mg	II	C	7	5	15.4 ± 2.10	9.11 ± 0.302	0.48(0.48-0.50)	1.42 ± 0.122
50 mg	II	C	GMR%	5	0.892 (8.8)	0.915 (8.5)	-	-
125 mg	II	D	1	6	44.0 ± 4.86	26.6 ± 3.99	0.48(0.48-0.65)	1.44 ± 0.208
125 mg	II	D	7	6	43.7 ± 5.49	27.5 ± 4.76)	0.48(0.48-0.48)	1.43 ± 0.186
125 mg	II	D	GMR%	6	0.990 (5.2)	1.03 (10.4	-	-
125 mg	II	E	1	6	42.5 ± 5.29	24.7 ± 2.80	0.48(0.48-0.48)	1.42 ± 0.213
125 mg	II	E	7	6	41.9 ± 4.47	26.0 ± 3.45	0.48(0.48-0.48)	1.34 ± 0.170
125 mg	II	E	GMR%	6	0.986 (8.8)	1.05 (23.3)	-	-
250 mg	II	F	1	6	78.9 ± 11.5	47.3 ± 9.10	0.48(0.48-0.48)	1.63 ± 0.130
250 mg	II	F	7	6	82.7 ± 13.8	49.4 ± 11.0	0.48(0.48-0.48)	1.65 ± 0.224
250 mg	II	F	GMR%	6	1.04 (5.9)	1.04 (24.8)	-	-
375 mg	III	G	1	6	105 ± 14.8	59.3 ± 11.5	0.48(0.48-0.75)	1.48 ± 0.147
375 mg	III	G	7	6	121 ± 16.2	70.2 ± 10.2	0.48(0.48-0.75)	1.85 ± 0.241
375 mg	III	G	GMR%	6	1.15 (9.7)	1.19 (15.2)	-	-
500 mg	III	H	1	6	162 ± 20.8	98.4 ± 23.4	0.48(0.48-0.52)	1.54 ± 0.232
500 mg	III	H	7	6	168 ± 20.2	103 ± 20.6	0.48(0.48-0.48)	1.68 ± 0.193
500 mg	III	H	GMR%	6	1.03 (3.9)	1.05 (11.7)	-	-
625 mg	III	I	1	6	187 ± 23.7	119 ± 24.1	0.48(0.48-0.50)	1.47 ± 0.186
625 mg	III	I	7	6	196 ± 28.7	117 ± 24.4	0.48(0.48-0.48)	1.73 ± 0.180
625 mg	III	I	GMR%	6	1.05 (6.8)	0.981 (22.3)	-	-

†Arithmetic Mean ± SD
‡ Median (Min – Max)
§Harmonic Mean ± pseudo SD
%GMR: Geometric Mean Ratio (%Geometric Coefficient of Variation) Ratio of Day 7 with to 1st

Pharmacokinetics in target population

About 73% of individuals in the integrated Phase 1, 2 and 3 popPK dataset were patients with active bacterial infection while the remaining 27% were healthy subjects. The effect of disease status (referred to as HLTH), was tested in the popPK analysis identified as significant only on imipenem V1. The effect of HLTH was small, with subjects with active bacterial infection having about 30% higher V1 for imipenem.

Simulated steady-state plasma PK parameters for imipenem and relebactam from the popPK model after multiple doses of 500-mg/250-mg IMI/REL as 30-minute IV infusions for 7 days are shown in Table 10.

Table 3. Population Pharmacokinetic-Derived Plasma Pharmacokinetic Parameters of Imipenem and REL Following Multiple Dose Administration of 500 mg/250 mg IMI/REL as 30-Minute IV Infusions Every 6 Hours in Patients

	Imipenem	Relebactam
AUC0-24hr (μM-hr)	500.0 (56.3)	390.5 (44.5)
Cmax (μM)	88.9 (62.1)	58.5 (44.9)
CL (L/hr)	13.4 (56.3)	7.4 (44.5)
t1/2 (hr)	1.0 (± 0.5)	1.2 (± 0.7)

(a) Geometric mean parameter estimates are shown for clearance, total AUC and total Cmax with their respective geometric CV% (coefficient of variation) values. Arithmetic mean (standard deviation) is shown for t1/2.

(b) Reported resulted are based on simulations with 500mg q6h imipenem and 250mg q6h of relebactam dosed as 30 minute IV infusion.

Source: [Ref. 5.3.5.3: 04VPMH: Table 23]

Renal impairment

Study MK-7655-005 was a dedicated renal impairment study to investigate the PK of a single dose of relebactam (125 mg) co-administered with imipenem/cilastatin 250 mg in subjects with mild (n=6), moderate (n=6) and severe (n=6) renal impairment, end-stage renal disease (ESRD; n=6) and matched healthy subjects (n=24). ESRD subjects received drug immediately after haemodialysis in one dosing period, and 30 minutes before haemodialysis in a second dosing period (7 days wash-out).

The subjects were included based on eGFR in ml/min/1.73 m2, but their Creatinine clearance was also calculated with the Cockcroft-Gault equation. The majority of subjects included had a high BMI (overweight), only 5 of the 24 subjects with RI had a BMI <25.

Table 4. Renal function of subjects included in study MK-7655-005 in initial categorisation.

Group	eGFR ml/min/1.73m2	eGRF range	Clcrea mean ml/min	Clcrea range	Inclusion range
Mild	63	54-71	70	62-87	50-80
Moderate	38	30-49	52	38-61	30-50
Severe	21	11-29	29	14-41	<30
ESRD	8	6-11	13	9-20	

For each of the analytes, the AUC was higher progressively with decreased renal function. A data presentation was included where the subjects were classified according to absolute GFR, and the AUC-ratio between renally impaired subjects and their healthy controls was 1.41, 2.56 and 5.80-fold in mild, moderate and severe RI. In subjects with ESRD, the AUC was high if given after dialysis (9.35-fold matched controls) but was removed by dialysis (1.75-fold matched controls when given pre-dialysis) (Table 12).

Figure 7. Individual values of relebactam Plasma AUC0-∞ versus Absolute eGFR Following the Administration of a Single IV Dose of 125 mg relebactam (30 min Infusion) in Combination With 250 mg imipenem/cilastatin in subjects with impaired renal function

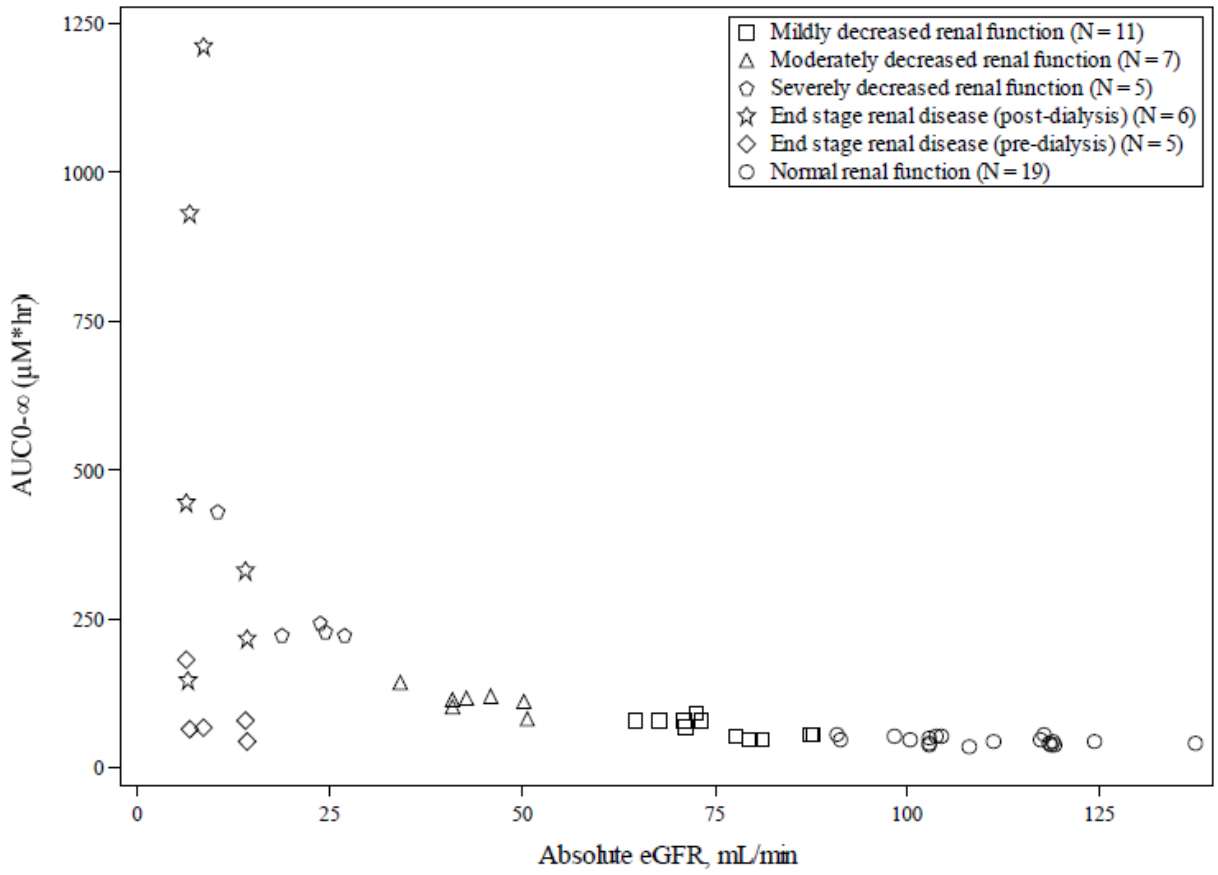


Table 5. PK results of study MK-7655-005 with renal impairment categorised according to absolute renal function.

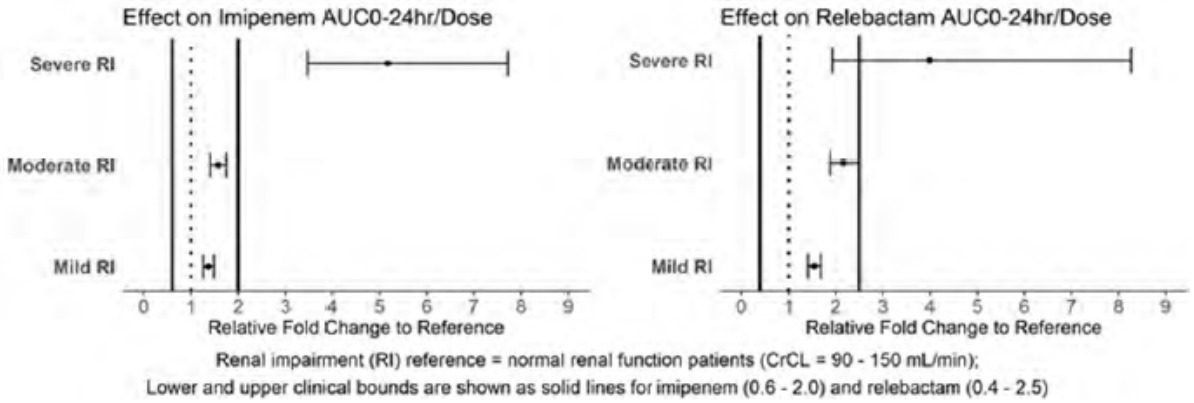
Pharmacokinetic Parameter	Renal Impairment			Healthy Control (Absolute eGFR ≥ 90)			Renal Impairment / Healtl	
	N	GM	95% CI	N	GM	95% CI	GMR §	90% CI §
Mildly decreased renal function (60 ≤ Absolute eGFR < 90)								
AUC0-∞ (µM*hr) †	11	63.5	(49.8, 80.9)	19	45.1	(38.0, 53.5)	1.41	(1.09, 1.82)
Ceoi (µM) †	11	22.2	(15.6, 31.7)	19	20.7	(16.1, 26.6)	1.07	(0.74, 1.56)
CLpred (mL/min) †	11	94.2	(73.9, 120)	19	133	(112, 157)	0.71	(0.55, 0.92)
Vzpred (L) †	11	19.9	(17.4, 22.7)	19	20.9	(19.0, 22.9)	0.95	(0.83, 1.10)
Apparent t1/2 (hr) ‡	11	2.32	32.3	19	1.88	15.4		
Moderately decreased renal function (30 ≤ Absolute eGFR < 60)								
AUC0-∞ (µM*hr) †	7	115	(85.8, 155)	19	45.1	(38.0, 53.5)	2.56	(1.91, 3.42)
Ceoi (µM) †	7	24.0	(15.6, 37.0)	19	20.7	(16.1, 26.6)	1.16	(0.76, 1.77)
CLpred (mL/min) †	7	51.9	(38.6, 69.7)	19	133	(112, 157)	0.39	(0.29, 0.52)
Vzpred (L) †	7	20.9	(17.8, 24.6)	19	20.9	(19.0, 22.9)	1.00	(0.85, 1.17)
Apparent t1/2 (hr) ‡	7	4.66	25.0	19	1.88	15.4		
Severely decreased renal function (Absolute eGFR < 30 not requiring dialysis)								
AUC0-∞ (µM*hr) †	5	261	(189, 361)	19	45.1	(38.0, 53.5)	5.80	(4.25, 7.91)
Ceoi (µM) †	5	23.5	(14.6, 37.9)	19	20.7	(16.1, 26.6)	1.14	(0.72, 1.79)
CLpred (mL/min) †	5	22.9	(16.5, 31.7)	19	133	(112, 157)	0.17	(0.13, 0.24)
Vzpred (L) †	5	19.2	(16.1, 22.9)	19	20.9	(19.0, 22.9)	0.92	(0.78, 1.09)
Apparent t1/2 (hr) ‡	5	9.41	25.1	19	1.88	15.4		

Pharmacokinetic Parameter	Renal Impairment			Healthy Control (Absolute eGFR ≥ 90)			Renal Impairment / Healtl	
	N	GM	95% CI	N	GM	95% CI	GMR §	90% CI §
End stage renal disease (post-dialysis) (Absolute eGFR < 15 requiring dialysis)								
AUC0-∞ (µM*hr) †	6	422	(302, 588)	19	45.1	(38.0, 53.5)	9.35	(6.92, 12.63)
Ceoi (µM) †	6	51.7	(31.8, 84.0)	19	20.7	(16.1, 26.6)	2.50	(1.61, 3.88)
CLpred (mL/min) †	6	14.2	(10.2, 19.8)	19	133	(112, 157)	0.11	(0.08, 0.14)
Vzpred (L) †	6	17.7	(14.8, 21.3)	19	20.9	(19.0, 22.9)	0.85	(0.72, 1.00)
Apparent t1/2 (hr) ‡	6	15.6	103.1	19	1.88	15.4		
End stage renal disease (pre-dialysis) (Absolute eGFR < 15 requiring dialysis)								
AUC0-∞ (µM*hr) †	5	78.9	(54.3, 115)	19	45.1	(38.0, 53.5)	1.75	(1.26, 2.43)
Ceoi (µM) †	6	18.8	(11.6, 30.6)	19	20.7	(16.1, 26.6)	0.91	(0.59, 1.41)
CLpred (mL/min) †	5	75.8	(52.1, 110)	19	133	(112, 157)	0.57	(0.41, 0.79)
Vzpred (L) †	5	61.7	(50.3, 75.6)	19	20.9	(19.0, 22.9)	2.95	(2.47, 3.53)
Apparent t1/2 (hr) ‡	5	10.5	100.6	19	1.88	15.4		

Corresponding analyses were performed for imipenem and cilastatin. The geometric mean ratios for imipenem were 1.19, 1.69 and 2.80 and for cilastatin 1.36, 2.22 and 7.16 in patients with mild, moderate and severe renal impairment, respectively.

The data from the renal impairment study was included together with data from a number of other studies in the dataset for the popPK modelling (see section 2.1.2). The model used the Cockcroft-Gault formula to estimate Clcrea, and Clcrea was found to be a significant covariate on both imipenem and relebactam clearance with a power function.

The effect of renal impairment on the PK of imipenem as well as relebactam according to the popPK model is displayed below:



The effect of severe RI on relebactam exposure was similar between the popPK model and the dedicated RI study (PN005), whereas the effect of severe renal impairment on imipenem exposure was predicted by the popPK model to be higher (5.17-fold) than observed in the study PN005 (2.51-fold).

Demographic data from multiple antibacterial clinical programs were used to define the variance-covariance matrix between CrCL and body weight and simulate a large dataset of virtual patients. From this simulated dataset, virtual subjects were randomly selected in order to generate population with different degrees of renal function, including augmented renal function (ARC). Simulations were performed in NONMENM using the final population PK model. The simulations performed included both unexplained between subject and residual error variability, as educated by the final PK model. PTA was simulated, according to the non-clinical PK/PD targets.

Table 6. Doses of Imipenem and Relebactam Chosen for PTA Simulations

Renal Impairment Category	Creatinine Clearance Range (mL/min)[†]	Dose of Imipenem/Relebactam*
Normal and Augmented Renal Function	90≤CrCL≤ 250	500/250 mg
Mild Renal Impairment	60≤CrCL< 90	400/200 mg
Moderate Renal Impairment	30≤CrCL< 60	300/150 mg
Severe Renal Impairment	15≤CrCL< 30	200/100 mg
End Stage Renal Disease[‡]	< 15	200/100 mg

*Administered every 6 hours by IV over 30 minutes

[†]Creatinine clearance calculated using the Cockroft-Gault equation

[‡]Imipenem/Relebactam to be administered only to end stage renal disease patients on hemodialysis and dose should be administered at intervals timed from the end of that hemodialysis session.

Special populations

The effect of hepatic impairment has not been studied.

A pharmacokinetic study comparing young and elderly healthy subjects as well as male and female subjects has been provided (8 subjects/group). On average, female subjects had a somewhat higher relebactam exposure than their male corresponding group (16% and 24% higher, respectively in the young and elderly groups). When comparing the effect of age in male and female elderly groups within the same gender, the elderly groups had higher mean exposures than young subjects of the same gender, increasing by 35% and

43%, respectively. Age was not found to be a clinically significant covariate in the popPK analysis, the age range in the dataset used for popPK modelling was 18-90 years with a median of 51 years.

Relebactam PK was studied in a set of Japanese subjects (n=19), and data were in line with previous data from non-Japanese subjects. Race was considered of exploratory interest in the popPK analysis. Most patients in the popPK-dataset were white (n=739), but the dataset included also black (n=32) and Asian (n=44) subjects. Because of small number of subjects from other races, race was not included as a covariate in both imipenem and REL popPK models. A post hoc assessment of between subject variability with race showed no evidence of relationship between race and PK parameters for either imipenem or relebactam.

In the popPK model, body weight was included as a covariate on V1 for both relebactam and imipenem, and on Cl for imipenem. The effect of body weight on relebactam or imipenem exposure due to body weight was however predicted to be minimal,

Pharmacokinetic interaction studies

- *In vitro*

An *in vitro* program was performed to assess the risk for relebactam being an inhibitor or inducer of drug metabolising enzymes and transporters.

The Cmax (end of infusion) measured after 7 days of treatment with 250 mg relebactam 4 times daily in study P 001 was 49 µM. With a protein binding of 22% (corresponding to unbound fraction of 78%), unbound Cmax would be 38 µM. Therefore, according to the EMA's guideline on the investigation of drug interactions, the concentration cut off for clinical relevance is calculated as 50 x Cmax,u which is in case of relebactam 1900 µM ~2 mM. This was the concentration that was included in most of *in vitro* drug interaction studies with relebactam which was in accordance with the EMA/CHMP guideline on drug interactions.

As the drug is given intravenously, interaction risks in the gastrointestinal tract or at first pass extraction is not expected.

No signs of CYP enzyme inhibition (direct and time-dependent) or induction was observed *in vitro* up to a relebactam concentrations of 2000 µM. Relebactam at concentrations up to 500 µM did not inhibit uptake of probe substrates for OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2K, BCRP and BSEP. Relebactam did not show inhibition of P-gp transporter at concentrations of up to 2000 µM in the *in vitro* experiments conducted with P-gp containing membrane vesicles and LLC-MDR1 cell monolayers.

No *in vitro* data on the potential for imipenem or cilastatin to act as an inhibitor or inducer of drug metabolising enzymes or transporters have been presented.

- *In vivo*

Relebactam was shown to be a substrate of OAT3, OAT4, MATE1 and MATE2K *in vitro*. An *in vivo* study with probenecid as an inhibitor of OAT transporters was performed. Study MK-7655A-019 was an open-label, randomized, 2-period, crossover trial to investigate the effect of probenecid on the single-dose PK of relebactam (primary objective) and imipenem. 14 healthy 15 healthy subjects were included, and each subject received the following treatments in a randomized order: 1) single IV dose of 250-mg imipenem/cilastatin/relebactam; and 2) single oral dose of 1 g oral probenecid administered 1 hour prior to a single IV dose of 250-mg imipenem/cilastatin/relebactam. The washout interval between treatments was at least 7 days.

Relebactam exposure (AUC) was 1.24-fold (90% CI 1.19, 1.28) higher following administration with probenecid. Imipenem AUCs were approximately 1.16-fold (90% CI (1.13, 1.20) higher following administration with probenecid.

In the ascending dose study P001V01, healthy subjects received relebactam and imipenem/cilastatin separately and in combination. An analysis of the 2-way drug interactions between REL and IMI (as individual components, imipenem and cilastatin) showed similar PK of the analytes when administered alone or in combination. Exposure of relebactam was similar with or without co-infusion of imipenem/cilastatin, the AUC0-∞ a geometric mean ratio (GMR) (90% CI) for 500 mg REL + 500 mg IMI compared to 500 mg REL alone were 1.02 (0.97, 1.06). Exposure of imipenem was similar with or without co-infusion of REL. The AUC0-∞ for the 500 mg REL + 500 mg IMI / 500 mg IMI alone comparisons was 1.03 (0.95, 1.12), and the corresponding ratio for cilastatin was 0.91 (0.87, 0.95).

The Recarbrio SmPC mentions two additional potential interactions, with ganciclovir and valproic acid.

2.4.3. Pharmacodynamics

The Applicant has performed a number of *in vitro* and *in vivo* PD and PK/PD studies. This section highlights the studies that describe the *in vitro* activity of relebactam, the potentiation of imipenem activity by the addition of relebactam *in vitro* and *in vivo* and the most important studies and analyses for dose selection of the single components of the fixed-dose-combination (FDC). It should be noted that because of the limited clinical development programme performed for this product in keeping with what is described in the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (EMA/CHMP/351889/2013) for products that are candidates to address an unmet medical need, the PK/PD analyses incorporating non-clinical PK/PD data and patient PK data is considered pivotal for dose selection.

Mechanism of action

Imipenem (IPM) 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 is stable to the majority of serine β-lactamases.

Cilastatin (CIL) is a renal dehydropeptidase inhibitor that limits the renal metabolism of IPM. CIL does not have antibacterial activity.

Relebactam (REL) is a novel 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.

Primary and Secondary pharmacology

Primary pharmacology – *in vitro*

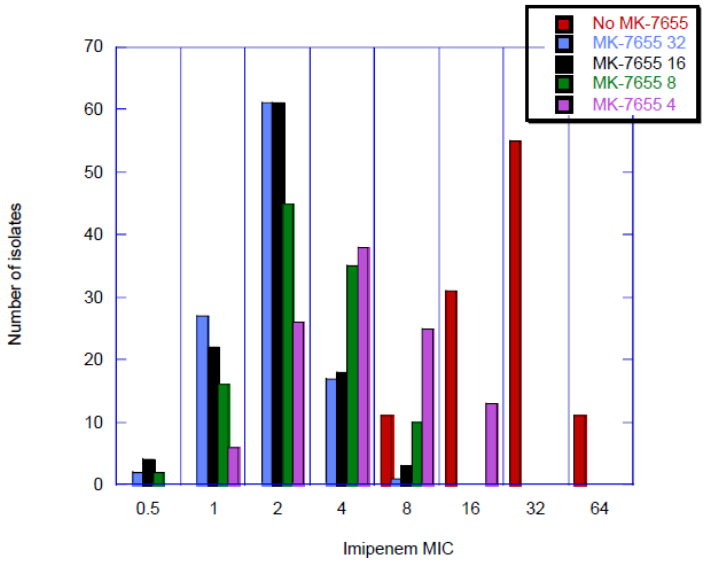
In vitro activity studies

In vitro susceptibility testing was conducted with imipenem/REL by testing varying concentrations of imipenem in the presence of a fixed concentration of 4 µg/mL REL. The Applicant has in general used CLSI susceptibility testing interpretive criteria in the dossier, unless otherwise stated.

In enzyme inactivation studies for REL against β-lactamase enzymes it was shown that REL is a time-dependent inhibitor of the carbapenem-hydrolysing β-lactamases KPC-2 and KPC-3 (belonging to Ambler class A) and the *Pseudomonas*-derived cephalosporinase PDC-1 (belonging to Ambler class C). The AmpC-enzyme PDC is the β-lactamase responsible for resistance in the majority of imipenem-resistant *P. aeruginosa*. REL furthermore inhibits other class A and class C enzymes.

Imipenem MICs in combination with various REL concentrations were evaluated against a panel of 108 clinical isolates of *P. aeruginosa* non-susceptible to IMI (CLSI interpretive criteria). The figure below shows the distribution of imipenem MIC values when different concentrations of REL were tested.

Figure PD1. Imipenem MIC distribution in presence and absence of various concentrations of REL (MK-7655) in imipenem-nonsusceptible *P. aeruginosa*



Imipenem MICs in combination with various REL concentrations were further evaluated against a panel of 76 KPC-producing Enterobacteriaceae. Against this panel a REL concentration of 4 µg/mL was sufficient to render 96% of the isolates susceptible interpreted with the CLSI breakpoint for susceptibility for IMI (1 µg/mL), see table below.

Table PD1. Imipenem MIC and susceptibility parameters when combined with REL in an expanded panel of KPC-expressing clinical isolates

	[1] Imipenem Minimum Inhibitory Concentration in Combination with MK-7655				
	No addition	32 µg/mL MK-7655	16 µg/mL MK-7655	8 µg/mL MK-7655	4 µg/mL MK-7655
[2] Number of imipenem susceptible isolates	4	75	74	73	73
[3] Percentage of imipenem-susceptible isolates	5	99	97	96	96
Imipenem MIC_{50} (µg/mL)	16	≤ 0.125	0.25	0.25	0.25
Imipenem MIC_{90} (µg/mL)	64	0.5	0.5	1	1
[4] Imipenem MIC range (µg/mL)	0.25 to > 256	≤ 0.125 to 4	≤ 0.125 to 4	≤ 0.125 to 4	≤ 0.125 to 4

1 Data are from 73 *K. pneumoniae*, 1 *E. coli*, 1 *C. freundii*, and 1 *E. cloacae*.

2 Number of imipenem-susceptible isolates, where the MIC ≤ 1 µg/mL.

3 Percentage of imipenem-susceptible isolates, where the MIC ≤ 1 µg/mL.

4 Total number of isolates = 76.

MIC_{50} = the lowest concentration of the antibiotic at which 50% of the isolates were inhibited; MIC_{90} = the lowest concentration of the antibiotic at which 90% of the isolates were inhibited; µg/mL = microgram per milliliter

Against a panel of 77 non-KPC-expressing Enterobacteriaceae clinical isolates the percentage of susceptible isolates (up to 1 µg/mL) increased from 88% with IMI alone to 99% with the addition of 4 to 32 µg/mL REL (data not shown). Both ESBL and plasmid-borne AmpC enzymes were represented in this panel, alone and in combination. Some isolates had permeability mutations contributing to higher imipenem MIC values.

Imipenem and imipenem/REL susceptibility were evaluated in large panels of *P. aeruginosa* isolates from the SMART global surveillance program from 2009 to 2016. There were only small changes in susceptibility profiles over the years. A summary from 2016 is shown in the table below:

Table PD2. Distribution of imipenem MICs for *P. aeruginosa* isolates from the SMART global surveillance program for imipenem alone and imipenem combined with 4 µg/mL of REL

SMART Study (N)			MIC (µg/mL)										
			≤ 0.06	0.125	0.25	0.5	1	2	4	8	16	32	≥ 64
SMART 2016 (6165)	IMI	N (%)	[a]ND	[a]ND	[a]ND	[b]925 (15.0%)	2593 (42.1%)	634 (10.3%)	278 (4.5%)	567 (9.2%)	671 (10.9%)	[c]497 (8.1%)	[c]ND
		Cumul. freq. (%)	[a]ND	[a]ND	[a]ND	15.0	57.1	67.3	71.9	81.1	91.9	100.0	100.0
	IMI/ REL	N (%)	49 (0.8%)	169 (2.7%)	1875 (30.4%)	2299 (37.3%)	564 (9.1%)	586 (9.5%)	154 (2.5%)	92 (1.5%)	68 (1.1%)	[c]309 (5.0%)	[c]ND
		Cumul. freq. (%)	0.8	3.5	33.9	71.2	80.4%	89.9	92.4	93.9	95.0	100.0	100.0

a This MIC value was not tested.

b This value is for ≥ 0.5 µg/mL, since MIC values < 0.5 µg/mL were not tested.

c This value is for ≥ 32 µg/mL, since MIC values ≥ 64 µg/mL were not tested.

CLSI = Clinical Laboratory Standards Institute; Cumul. = cumulative; EUCAST = European Committee on Antimicrobial Susceptibility Testing; freq. = frequency; IMI = imipenem; IMI/REL = imipenem/relebactam, MIC = minimum inhibitory concentration; µg/mL = microgram per milliliter; N = number; ND = not determined; Sus. = susceptibility

Source: Reports PD019, PD022, PD034, and PD035 [Sec. 2.6.3.1]; Merck notebooks NB-youngkat-0375403-0020 and NB-youngkat-0375403-0029; Young et al, 2018 [Ref. 4.3: 04ZX2M].

The tables below depict pooled imipenem-non-susceptible isolates from all sources. Note that % susceptibility relates to IMI breakpoints and that EUCAST breakpoint for susceptibility for IMI relates to high dose frequent therapy (1 gram q6h).

Table PD3. Effect of REL on the cumulative percent of susceptibility of a panel of imipenem nonsusceptible *P. aeruginosa* isolates from the SMART global surveillance program

Imipenem MIC (µg/mL)	Number	Number Susceptible to Imipenem[a] with REL[b] (CLSI)	% Susceptible to Imipenem[a] with REL[b] (CLSI)	Number Susceptible to Imipenem[c] with REL[b] (EUCAST)	% Susceptible to Imipenem[c] with REL[b] (EUCAST)	Cumulative Number	Cumulative Number Susceptible to Imipenem/ REL (CLSI)	Cumulative % Susceptible to Imipenem/ REL (CLSI)	Cumulative Number Susceptible to Imipenem/ REL (EUCAST)[f]	Cumulative % Susceptible to Imipenem/ REL (EUCAST)[f]
4	648	639	98.6%	648	100.0%	648	639	98.6%	NA[e]	NA[e]
8	1228	1159	94.4%	1195	97.3%	1876	1798	95.8%	1195	97.3%
16	1527	1143	74.9%	1393	91.2%	3403	2941	86.4%	2588	93.9%
32	675	192	28.4%	408	60.4%	4078	3133	76.8%	2996	87.3%
64[d]	455	12	2.6%	19	4.2%	4533	3145	69.4%	3015	77.6%
128	43	1	2.3%	1	2.3%	4576	3146	68.8%	3016	76.8%
>128	74	1	1.4%	2	2.7%	4650	3147	67.7%	3018	75.4%
Total	**4650**									

a CLSI breakpoint for imipenem is 2 µg/mL.
b In vitro susceptibility concentration for REL is 4 µg/mL.
c EUCAST breakpoint for imipenem is 4 mg/L or 4 µg/mL.
d The Imipenem MIC 64 µg/mL data row includes isolates with MIC values ≥ 32 µg/mL.
e Not applicable for the combination of imipenem/REL at 4 µg/mL imipenem.
f The total N = 4002 for cumulative number susceptible to imipenem/REL and for cumulative percent susceptible to imipenem/REL by EUCAST criteria.

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = minimum inhibitory concentration; µg/mL = microgram per milliliter; mg/L = milligram per liter; NA = not applicable

Because of the stability of imipenem alone against many class A and C β-lactamase-producing Enterobacteriaceae the beneficial effect of adding REL to imipenem is most notable for isolates producing KPC (table below).

Table PD4. Imipenem MICs for KPC-producing Enterobacteriaceae (SMART global surveillance 2015 and 2016; N=661) for imipenem alone and imipenem/REL

Drug	MIC_{50}	MIC_{90}	MIC Range	MIC Mode
Imipenem	≥32	≥32	≤0.5 - ≥32	≥32
Imipenem/ REL	0.25	1	≤0.06 - 8	0.25

Only two- to four-fold shifts of MIC_{50} and MIC_{90} were seen when REL was added to imipenem against Enterobacteriaceae producing ESBLs and AmpC β-lactamases (table below).

Table PD5. Imipenem MICs for ESBL and/or AmpC-producing Enterobacteriaceae (SMART global surveillance 2016) for imipenem alone and imipenem/REL

Year	Phenotype	Drug	N	MIC_{50} µg/mL	MIC_{90} µg/mL	Minimum µg/mL	Maximum µg/mL
2016	ESBL	Imipenem	5428	≤ 0.5	1	≤ 0.5	≥ 32
2016	ESBL	Imipenem/REL	5428	0.12	0.5	≤ 0.06	≥ 32
2016	AmpC	Imipenem	984	0.5	4	≤ 0.5	≥ 32
2016	AmpC	Imipenem/REL	984	0.12	1	≤ 0.06	≥ 32

In studies with anaerobic organisms REL did generally not enhance the activity of imipenem. Imipenem/REL (as well as imipenem alone) is however expected to cover anaerobic organisms in typical mixed infections such as complicated intraabdominal infections (cIAI).

Resistance to imipenem/REL

Imipenem/REL is not active against isolates that produce class B β-lactamases and class D carbapenemases. Expression of certain alleles of the class A β-lactamase Guiana extended-spectrum β- lactamase (GES) and overexpression of PDC coupled with loss of imipenem entry porin OprD may confer resistance to imipenem/REL in *P. aeruginosa*. The expression of efflux pumps in *P. aeruginosa* does not affect activity of either imipenem or REL. Mechanisms of bacterial resistance that could decrease the antibacterial activity of imipenem/REL in Enterobacteriaceae include porin mutations affecting outer membrane permeability.

Laboratory selection of resistance

To determine frequencies of resistance and select representative resistant mutants, two sets of studies were performed (using Efficiency of plating [EOP] and Luria-Delbruck fluctuation test). All selection concentrations were based around and above the breakpoint for imipenem with REL concentrations in most experiments set to 4 μg/mL.

In vitro selection for resistance was conducted in 4 clinical isolates of *P. aeruginosa* with constitutive or inducible AmpC and OprD +/- and 5 isolates of *K. pneumoniae* producing class A or C enzymes, including KPC.

In *P. aeruginosa*, mutants were not selected against all strains and at all concentrations of imipenem tested yielding a frequency below 2×10^{-9}. In experiments where mutants were selected the resistance frequencies were between 2×10^{-8} to 4×10^{-9}. In these mutants the imipenem and imipenem/REL MICs compared to the parent strain were increased 1- to 2-fold and 4-fold, respectively.

In *K. pneumoniae*, at the lowest concentration of imipenem tested (all concentrations were at or above the IMI/REL MIC for the respective isolate) mutants were selected at frequencies of, at the lowest, 2×10^{-5}. At the highest imipenem concentration tested (4 μg/mL; corresponding to 4-fold the CLSI breakpoint for imipenem) no resistant mutants were selected for two strains yielding a frequency of below 5×10^{-9}. For the other strains, resistance mutants were selected at frequencies of $\sim 2 \times 10^{-8}$. These mutants had imipenem and imipenem/REL MICs compared to the parent strain that were increased 1- to >16-fold and 2- to 32-fold, respectively.

In one of the isolates of *K. pneumoniae* expressing a KPC-2 with a very high MIC to imipenem, resistant variants were selected but the mechanism of resistance was not confirmed by whole genome sequencing. For one of the two other KPC-expressing Enterobacteriaceae for which mutants could be selected at 4× the breakpoint concentration of imipenem no regrowth was seen in hollow fibre studies for up to 72 hours even at concentrations of REL one-half the clinical dose.

The mechanism underlying the increased concentration of REL required to restore susceptibility to imipenem in the mutants selected to the combination of imipenem and REL was investigated but remains unknown; however, no differences between the selected mutant and parent strains were observed for β-lactamase expression, β-lactamase induction by imipenem, or REL inhibition of β-lactamase activity.

Post-antibiotic effect

A post-antibiotic effect (PAE) of 2 h was noted for sub-MICs of imipenem in the combination with 4 mg/L of REL. The PAE noted after exposure to IMI and REL followed by washout was prolonged to up to 6 h when sub-MICs of imipenem alone was added again after washout of imipenem and REL, reflecting a retained inhibitory effect against β-lactamases (post-inhibitor effect [PIE]) despite absence of REL in the medium.

Effects of human body fluids on susceptibility to imipenem/REL

The *in vitro* activity of imipenem/REL was similar in the presence of pulmonary surfactant, urine or serum. There was a trend to increased MICs at lower pH values.

Hollow-fibre infection model (HFIM) studies

In an HFIM-study the antibacterial activity and suppression of resistance of imipenem and imipenem/REL were investigated against four imipenem-resistant strains (one *K. pneumoniae* and three *P. aeruginosa*). For imipenem, 30-minute infusions simulating either a human 500 mg (low) or 1,000 mg (high) doses every 6 h were used. For REL, a dose of 500 mg (given over 30 min) every 6 h was simulated. Imipenem/REL considerably reduced the bacterial burden at 24 h, while failure with imipenem alone was seen against all isolates. Sustained suppression of bacterial growth at 72 h was achieved with simulated doses of 500 mg imipenem plus 500 mg REL in one *K. pneumoniae* and one *P. aeruginosa* strain. Against one *P. aeruginosa* strain regrowth was seen at 72 h with the imipenem low-dose regimen but not with the high-dose regimen. Against one *P. aeruginosa* strain, regrowth was detected at 48 h for both doses. The MIC results of the strain tested before and after the experiment are shown in the table below. Note that the imipenem MICs for the 3 daughter isolates were not reduced as effectively by REL as those for the parent isolate.

Table PD6. Post-HFIM susceptibility testing results for PA24226 and three random isolates after regrowth was observed

	MIC (mg/liter)[a]				
Isolate	IPM	IPM with MK (4 mg/liter)	IPM with MK (8 mg/liter)	IPM with MK (16 mg/liter)	IPM with MK (32 mg/liter)
Parent	32	1	1	0.5	0.5
Daughter A	64	4	2	2	2
Daughter B	64	4	2	2	2
Daughter C	64	4	2	2	2

[a] IPM, imipenem; MK, MK-7655.

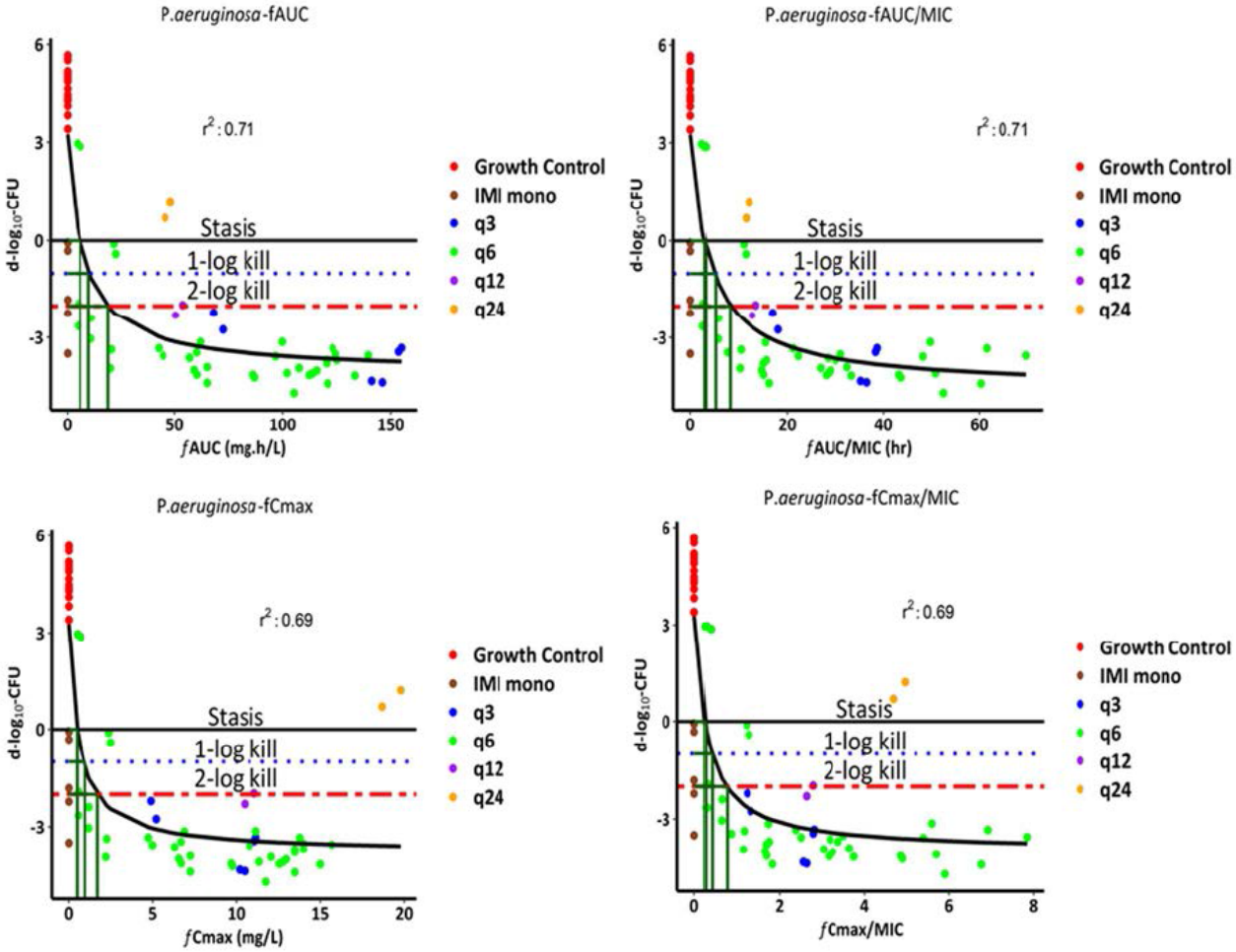
Free-drug exposures corresponding to clinical doses of imipenem 500 mg, q6h with and without REL 125 or 250 mg, q6h were further evaluated against imipenem-resistant strains of *P. aeruginosa* and Enterobacteriaceae over 70 h in a hollow-fibre system. Both 125 mg and 250 mg doses of REL showed rapid and sustained bactericidal activity against 3/4 *Pseudomonas* strains (IMI MICs 16 to 32 µg/mL; IMI/REL MICs 2 to 8 µg/mL). Against these strains, the bacterial CFU count was below the detectable limit of 10 CFU/mL in 15 to 30 h and a 4-fold $\log_{10}$ reduction versus the starting inoculum was observed. Against one strain of *P. aeruginosa* (imipenem MIC 64 µg/mL; imipenem/REL MICs 16 µg/mL) the lower dose of REL was not efficacious and it took >50 h for imipenem + REL 250 mg to reduce the colony count to below detectable limits.

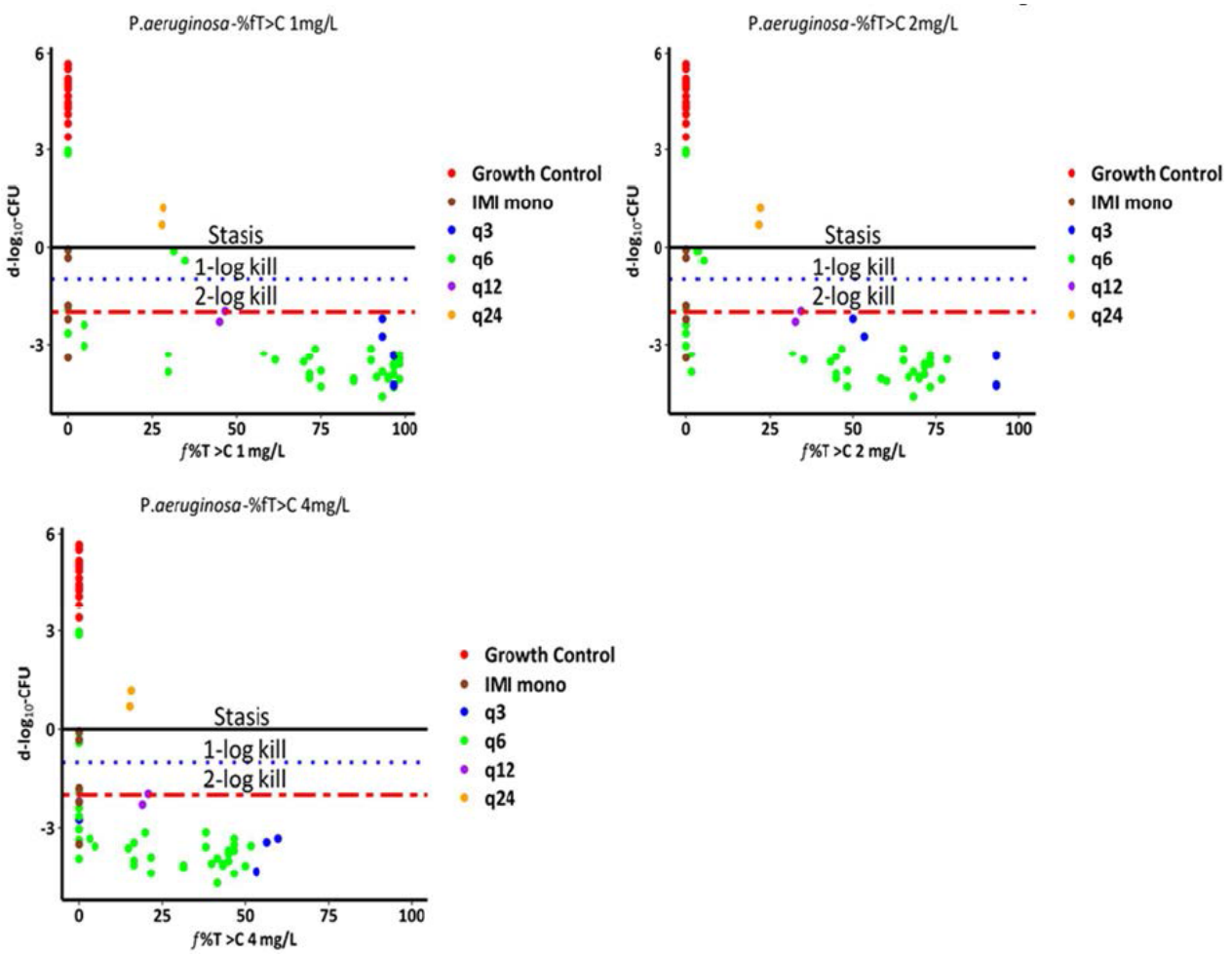
Imipenem in combination with both doses of REL showed rapid and sustained bactericidal activity against a KPC-producing *K. pneumoniae* strain with greater than 5-fold $\log_{10}$ reduction in CFU within 6 to 12 h. Additionally, against 10 Enterobacteriaceae strains producing various class A and/or class C enzymes

imipenem and REL 250 mg (125 mg not tested) was efficacious against all strains with colony count reductions below the limit of detection and no grow-back. Against two of the strains that displayed lowest imipenem MICs (4 and 8 µg/mL, respectively), imipenem alone was as efficacious as the combination.

In the same study the relationship between different PK/PD indices and REL´s activity was determined (figure below). The index *f*AUC/MIC and *f*AUC showed the best relationship with the activity of REL against *P. aeruginosa*. The REL *f*AUC/MIC target values associated with stasis, 1-$\log_{10}$ and 2-$\log_{10}$ bacterial load reduction for *P. aeruginosa* in the hollow fibre model were 2.9, 4.8 and 8.2, respectively.

Figure PD2a. PK/PD relationship of REL based on HFIM data for 5 strains of *P. aeruginosa*





The Applicant has not performed full dose-ranging for Enterobacteriaceae but used the clinical dosing regimen in these experiments. The E_{max} model fit for log_{10} bacterial load reduction versus AUC/MIC based on the *P. aeruginosa* HFIM data overlaid on the pooled Enterobacteriaceae HFIM data (figure below) shows that the target values at stasis, 1-log, and 2-log kill for Enterobacteriaceae are expected to be less than that for *P. aeruginosa* in the HFIM experiments because the data-points for bacterial reduction of Enterobacteriaceae are below the *P. aeruginosa* curve. This conflicts however with the findings in the neutropenic thigh model in which higher targets seems to be needed for *K. pneumoniae* than *P. aeruginosa* to achieve similar antibacterial effects (see below).

Figure PD2b. PK/PD relationship of REL based on HFIM data for 8 strains of Enterobacteriaceae

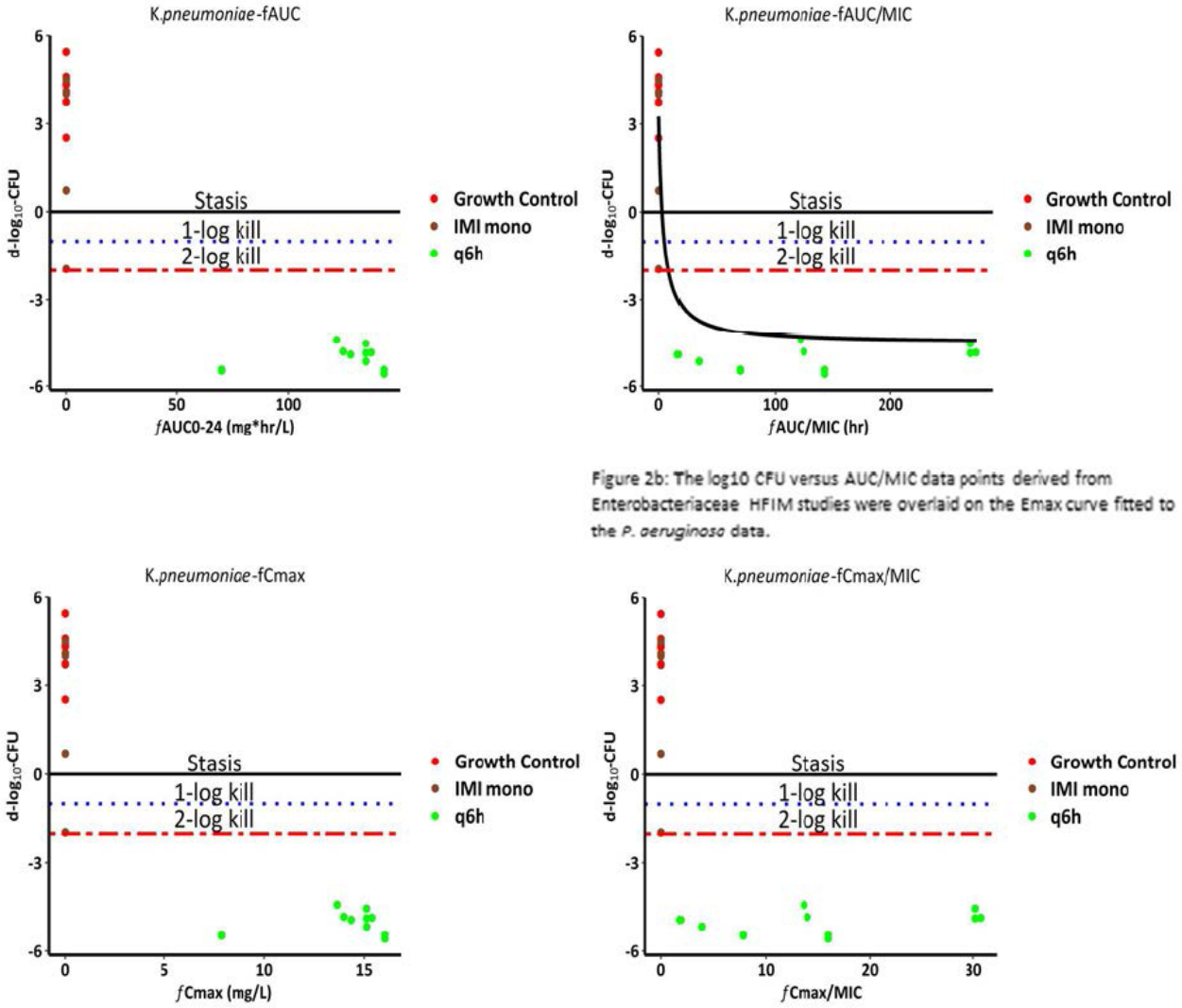
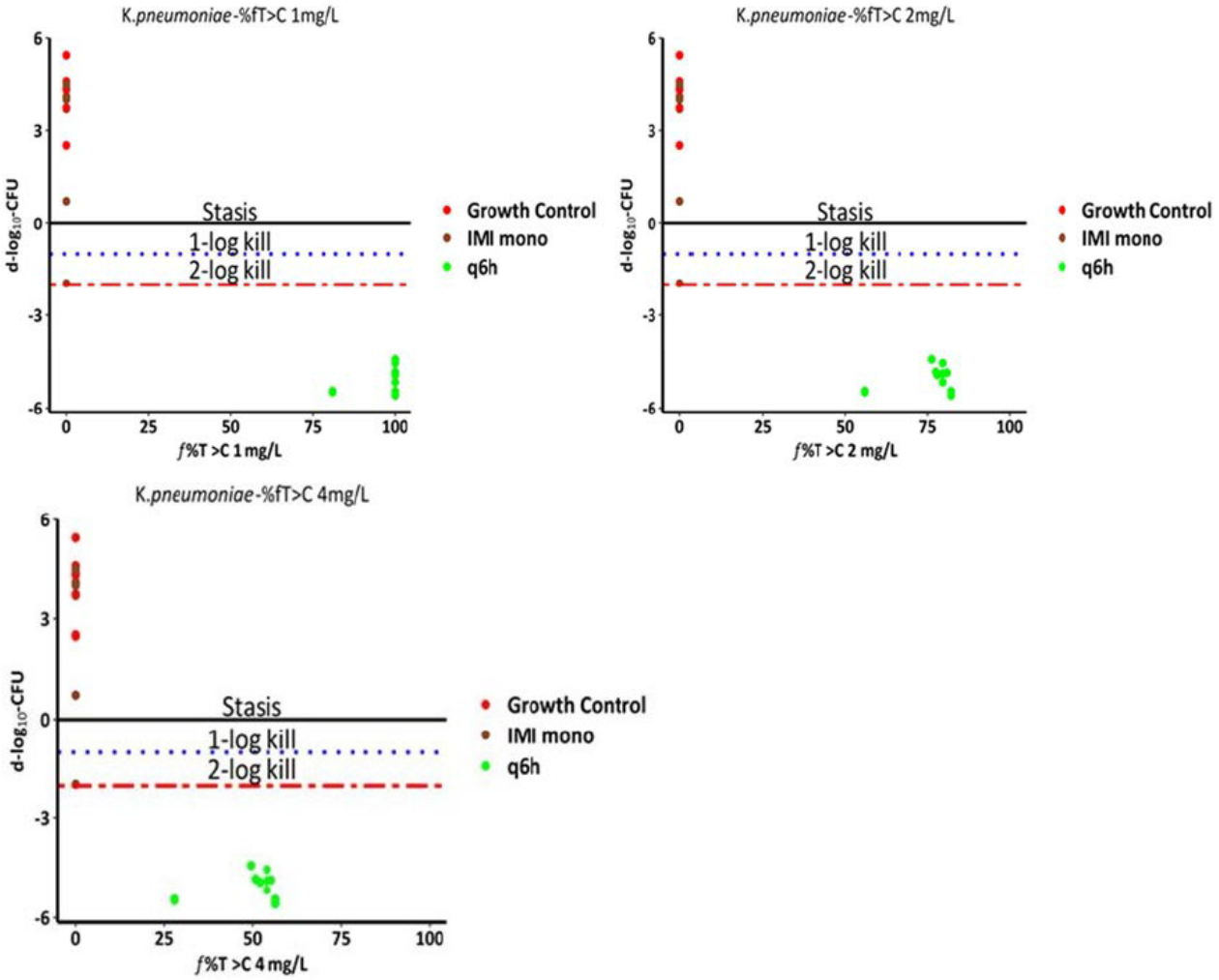


Figure 2b: The log10 CFU versus AUC/MIC data points derived from Enterobacteriaceae HFIM studies were overlaid on the Emax curve fitted to the *P. aeruginosa* data.

The $\log_{10}$ CFU versus AUC/MIC data points derived from Enterobacteriaceae HFIM studies were overlaid on the Emax curve fitted to the *P. aeruginosa data*



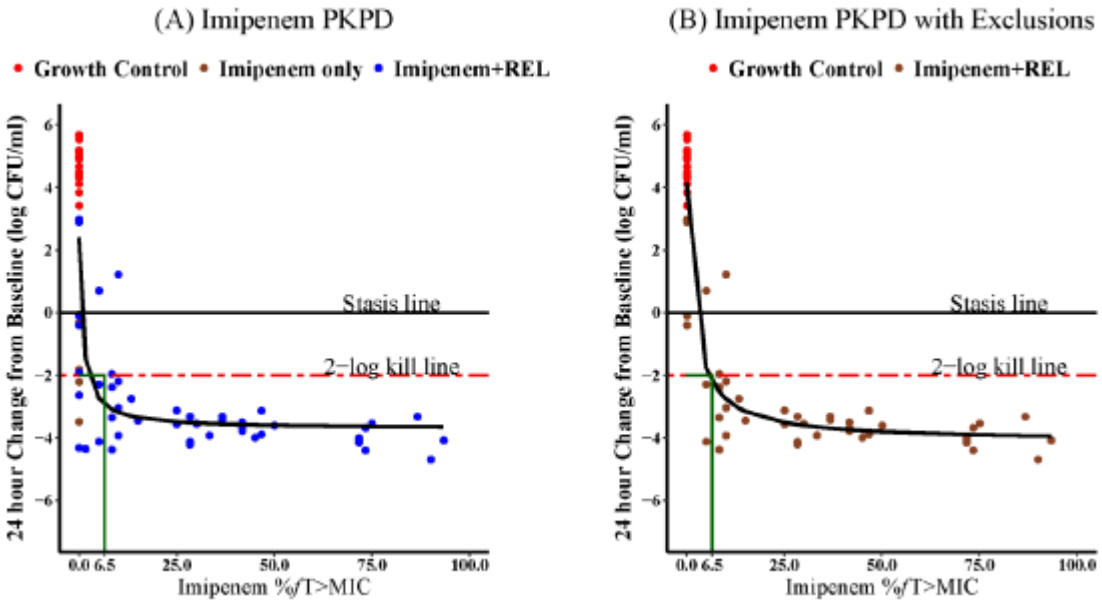
The data from this HFIM study against strains of *P. aeruginosa* was in addition used to evaluate the magnitude of the pharmacokinetic-pharmacodynamic target (PDT) for imipenem needed to achieve 2-$\log_{10}$ kill. It is well established that efficacy for imipenem and other β-lactam antibacterial agents is driven by the percentage of time during the dosing interval that the unbound fraction of the antibacterial is above the MIC (%*f*T>MIC). For carbapenems, literature information suggests that 20% *f*T>MIC is required for bacteriostatic effect, and at least 30% to 40% *f*T>MIC is required to achieve 1- to 2-log kill *in vivo* animal models. The Applicant proposes that the magnitude of the β-lactam target may be different when combined with a BLI. This was therefore investigated. Since sub-therapeutic REL doses were also studied, the REL potentiated IimipenemMI MIC was the imipenem MIC at the average concentration of REL (C_{avg}) achieved in each study (being approximately 4 mg/L in the REL 250 mg q6h regime which is proposed to be used generally in imipenem/REL MIC determinations).

IMI and IMI/REL both showed efficacy and rapid bacterial killing with time in HFIM even when IMI doses were substantially subtherapeutic. Due to this, there was a very steep relationship between E and IMI %*f*T>MIC. This resulted in difficulty identifying $TMIC_{50}$ which was estimated with a p-value >0.05 and thus was statistically not significant. To mitigate the $TMIC_{50}$ identifiability issue, ten experimental runs with good response near 0%*f*T>MIC were excluded in an alternate sensitivity analysis. Specifically, the experimental runs mentioned were excluded due to significant change in bacterial burden at 24 hours from baseline even with very low IMI %*f*T>MIC (table below).

Experiment	*P.aeruginosa* Strain	Imipenem Regimen	REL Regimen	ID in Dataset	%T>MIC	24 hr Change in log10(CFU/mL) from Baseline
11007	24227	500 mg q6h	0 mg	15	0	-3.5
11007	24227	500 mg q6h	0 mg	16	0	-2.2
11011	24228	500 mg q6h	0 mg	30	0	-0.3
11011	24228	500 mg q6h	0 mg	31	0	-1.8
12001	24226	500 mg q6h	0 mg	36	0	-0.06
12001	24226	500 mg q6h	0 mg	37	0	-0.07
12003	24226	60 mg q3h	125 mg q3h	52	0	-4.3
12003	24226	60 mg q3h	125 mg q3h	53	1.6	-4.3
12005	24227	200 q6h	13 q6h	64	0	-2.6
12005	24227	200 q6h	13 q6h	65	0	-1.9

The parameter estimates and results of the E_{max} model fit after exclusion are shown in the table and figure below. Based on this analysis, the value of IMI % *f*T>MIC that is required for 2-log kill is about 6.5%.

	Estimate	SE	p-value
E_0	4.2	0.3	<2e-16
E_{max}	-8.3	0.4	<2e-17
$TMIC_{50}$	2.0	0.8	0.012



Based on the relationship between IMI % *f*T>MIC and PD effect, if one considers all HFIM experiment data, the IMI % *f*T>MIC required for 2-log kill is approximately 3%. With exclusions to allow model estimation, the estimated IMI % *f*T>MIC target of 6.5% for 2-log kill is according the Applicant therefore a conservative estimate of the IMI % *f*T>MIC requirement. In the HFIM, when the effect of REL is considered, the IMI % fT>MIC requirement was lowered significantly. This effect could according the Applicant be attributed to the

fact that the imipenem MIC in presence of REL is assessed at C_{avg} of REL, while in reality the concentration of REL fluctuates with time and in some strains exhibits a post-inhibitor effect. Using C_{avg} of REL may not fully capture the impact of REL on the potency of imipenem under dynamically changing concentration profiles thus producing higher potentiated MIC values and corresponding lower % *f*T>MIC values.

Chemostat infection model studies

Furthermore, the antibacterial effect of imipenem/REL was studied against Enterobacteriaceae and *P. aeruginosa* in a one compartment *in vitro* pharmacokinetic model over 168 h. One wild type *E. coli* strain, three *K. pneumoniae* strains (one AmpC producer, two KPC producers) and four strains of *P. aeruginosa* (one wild type, one isogenic mutant, one with porin loss and one with porin loss and AmpC beta-lactamase production) were employed. Imipenem/REL MICs were 0.06 to 0.5 mg/L for the Enterobacteriaceae strains and 0.25 to 1.0 mg/L for *P. aeruginosa*. Free drug serum concentrations of imipenem 500 mg q6h plus REL 250 mg q6h were simulated. In addition, two strains of *P. aeruginosa* were exposed to imipenem plus REL plus amikacin.

The objectives of this study were (1.) to describe the long term antibacterial effects against a range of strains with an without beta-lactamase production, (2.) to assess the risk of emergence of resistance by studying changes in population profiles and (3.) to assess the impact of the addition of amikacin to imipenem/REL simulations in terms of antibacterial effect and emergence of resistance.

The Enterobacteriaceae strains were all rapidly killed showing a 3 $\log_{10}$ reduction in colony count by 6 h. The wild type *E. coli* strain and *K. pneumoniae* 42421 (KPC) were eradicated from the model by 6 h. The other KPC-producing strain *K. pneumoniae* 62267 was eliminated by 24 h and the AmpC-producing strain with porin loss (*K. pneumoniae* 47929) also showed a 3 $\log_{10}$ reduction in viable count at 6 h and was eradicated by 96 h.

The *P. aeruginosa* strains all demonstrated a 3-4 $\log_{10}$ reduction in bacterial count by 6 h however only one strain was eradicated from the model - *P. aeruginosa* 17286 (a meropenem isogenic mutant) which was eliminated from the model by 96 h. The wild type strain *P. aeruginosa* 38475 and the *P. aeruginosa* strains with porin loss (*P. aeruginosa* 62267) and/or AmpC production (*P. aeruginosa* 47235) bacterial counts increased from 2 $\log_{10}$ at 6 h to 3-4 $\log_{10}$ at 168 h.

No changes in population analysis profiles were seen for the *E. coli* and *K. pneumoniae* strains. One *P. aeruginosa* strain was eliminated from the model and therefore no progeny grew. For the other three strains of *P. aeruginosa* a 2.5 to 4.5 $\log_{10}$ growth was seen on the recovery and x2 MIC imipenem plus REL plates at 168 h. No difference was observed between the parent and progeny imipenem plus REL MICs on subsequent testing.

Primary pharmacology - *In vivo*

IMI/REL evaluated in animal models of infection

The *in vivo* efficacy of IMI/REL was assessed in several murine models of infection. In initial studies, treatment followed shortly after infection (disseminated infection with *P. aeruginosa* or *K. pneumoniae* and pulmonary infection with *P. aeruginosa*):

Disseminated model of infection

Mice were infected by intra-peritoneal injection with 2.2×10^6 CFU of *P. aeruginosa* CLB 24228 (IMI MIC = 32; IMI/REL MIC = 8 µg/mL). REL was administered (10, 20, and 40 mg/kg/dose) in combination with IMI (5 mg/kg/dose) by continuous infusion for 60 minutes q6h for 24 hours. Treatment with this combination

resulted in 1.72, 3.13, and 3.73 $\log_{10}$ reduction in bacterial load in the spleen at REL doses of 10, 20, and 40 mg/kg, respectively. Mice treated with IMI alone only had a modest reduction in *P. aeruginosa* tissue burden (0.45 $\log_{10}$). A reduction of bacterial tissue burden by >3 $\log_{10}$ was achieved in the 20 mg/kg/dose treatment group where the peak concentration of REL in plasma reached 108 µM. This translates to a 24-hour plasma exposure of approximately 57.1 mg×hour/L REL.

Mice were infected by IP injection with 5.5×10^5 CFU of *K. pneumoniae* CL 6339 (IMI MIC = 64; IMI/REL MIC = 1 µg/mL). REL was administered (20, 40, and 80 mg/kg/dose) in combination with IMI (5 mg/kg/dose) by continuous infusion for 60 minutes q6h for 24 hours. Treatment with this combination resulted in 2.29, 3.06, and 2.69 $\log_{10}$ reduction in spleen bacterial load at REL doses of 20, 40, and 80 mg/kg, respectively. Mice treated with IMI alone had *K. pneumoniae* tissue burden equivalent to untreated animals. In this study a 2.29 $\log_{10}$ reduction of bacterial tissue burden was achieved in the 20 mg/kg/dose treatment group. This translates to a 24-hour plasma exposure of approximately 36.2 mg×hour/L REL.

Pulmonary infection model

The *in vivo* efficacy of REL was also evaluated in a pulmonary model of infection using the IMI-resistant *P. aeruginosa* strain CLB 24228. Each mouse was infected by intra-nasal inoculation with 1.4×10^5 CFU. REL was administered (20, 40, and 80 mg/kg/dose) in combination with IMI (5 mg/kg/dose) by continuous infusion for 60 minutes q6h for 24 hours. Treatment with this combination resulted in 2.37, 3.59, and 4.59 $\log_{10}$ reduction in bacterial load in the lung at REL doses of 20, 40, and 80 mg/kg, respectively. By way of comparison, mice treated with IMI alone had *P. aeruginosa* tissue burden equivalent to untreated animals. In this study, reduction of bacterial burden in the lung by 2.37 $\log_{10}$ CFU was achieved in the 20 mg/kg/dose treatment group. This translates to a 24-hour plasma exposure of approximately 37.0 mg×hour/L REL.

Delayed pulmonary infection model

The combination was further studied in a more clinically relevant model, a delayed therapy model of infection with *P. aeruginosa* with treatment initiated after the infection was already established. This model was adapted to a model earlier described in which a static response to therapy is considered predictive of clinical efficacy (Craig and Andes, 2008).

A total of three independent delayed treatment studies were performed. In the three studies, *P. aeruginosa* (with an imipenem MIC 32; imipenem/REL MIC 8 µg/mL) tissue burden was approximately 10^5 CFU at 16.5 hours post-infection and the bacterial load increased by >2 $\log_{10}$ CFU in untreated animals over the subsequent 24-hour period. In these studies, treatment with 5 mg/kg IMI alone had no significant effect. The dose of IMI is sub-therapeutic and approximately 13-fold lower than 500 mg equivalent humanized IMI dose in mouse (64 mg/kg). *P. aeruginosa* burden in these animals reached >7 $\log_{10}$ CFU in the lung. However, the combination of 5 mg/kg IMI together with 20 mg/kg REL had a static effect on *P. aeruginosa* tissue burden in this model. There was no significant increase in bacterial load in the lung compared to the burden at the start of therapy. Treatment regimens that combined 5 mg/kg IMI with either 40 or 80 mg/kg REL also imparted a static effect on *P. aeruginosa* burden in this model, while the combination of 5 mg/kg IMI with 10 mg/kg MK-7655 did not. The 24-hour plasma exposure of REL required to reach target efficacy (defined as a static effect on tissue burden which was reached with the 20 mg/kg REL dose) is 40.0, 63.3 and 42.0 mg×hour/L, respectively in the three independent studies. This 24-hour plasma exposure translates to a free drug $AUC_{0\text{-}24\ hr}$/MIC (potentiated) target of 4.0, 6.2 and 4.2, respectively.

Additional studies were performed to expand the strains examined. Nine strains of *P. aeruginosa* (imipenem MICs 16 to 64 µg/mL; imipenem/REL MICs 2 to 16 µg/mL) and two strains of *K. pneumoniae* (imipenem MICs 64; imipenem/REL MICs 0.25 to 0.5 µg/mL) were examined. Significant reduction in bacterial burden was

achieved for 10 of 11 *P. aeruginosa* and *K. pneumoniae* strains tested with sub-inhibitory IMI concentrations in combination with REL.

Overall, in all the delayed pulmonary infection model experiments, an average 24-hour plasma exposure to achieve stasis against strains of *P. aeruginosa* of 41.9 mg×hour/L (range 11.1 to 148) translates to a mean free drug $AUC_{0\text{-}24\ hr}$/MIC target of 4.0 h (range 1.0 to 14.6 h). In the 15 experiments, that each included in general five animals per dose level, the free drug $AUC_{0\text{-}24\ hr}$/MIC (potentiated) target was below 5.0 h in 12 of 15 studies and in the remaining three 6.2, 7.9 and 14.6 h, respectively. Strain CLB24228 was tested in six different experiments. It should be noted that the free drug $AUC_{0\text{-}24\ hr}$/MIC target had large within strain variation (1.1 to 6.2 h)

For the two strains of *K. pneumoniae* tested of which one was tested in two sets of experiments, the average 24-hour plasma exposure to achieve stasis was similar compare to the exposure needed for stasis against *P. aeruginosa* (41.4 mg×hour/L; range 20.5 to 81.3). However, possibly due to the lower IMI/REL MICs (potentiated) for the *Klebsiella* strains (0.25 to 0.5 µg/mL) compared to the *Pseudomonas* strains the free drug $AUC_{0\text{-}24\ hr}$/MIC to achieve stasis was several folds higher (70.5, 64.8 and 128.5, respectively). This would indicate that the relation between AUC/MIC is not constant regardless of potentiated MIC.

Murine thigh model

The PK/PD index best correlated to the activity of REL and PK/PD targets were explored in a neutropenic thigh infection model. Four strains of *P. aeruginosa* and two strains of *K. pneumonia* were studied. Neutropenic CD-1 mice were infected in each thigh 2 hours before treatment with an inoculum of approximately 5×10^6 CFU. The mice were treated with IMI every 2 hours (q2h) at lower or up to humanised doses in combination with REL in either a dose fractionation study or q2h for 24 hours and sacrificed for CFU determinations.

For REL, various PK/PD indices such as area under the concentration-time curve (AUC), $\%T > C_T$ (percent time above threshold concentration), and peak concentrations were correlated with efficacy as measured by change in bacterial burden (change in log CFU). The REL PK parameter that correlated best with efficacy across both *P. aeruginosa* and *K. pneumonia* was *f*AUC/MIC as demonstrated by the figures below when half or the full humanised dose of IMI was used in the experiments. The derived stasis,1-log kill and 2-log kill *f*AUC/MIC targets for *P. aeruginosa* were 3.3, 4.3 and 7, respectively. Notably, approximately 10-fold higher *f*AUC/MIC targets are needed for *K. pneumoniae* than *P. aeruginosa* to achieve similar antibacterial effects.

Figure PD3a. PK/PD relationship of REL in the neutropenic mouse thigh infection model at IMI 8 mg/kg and 15.9 mg/kg for *P. aeruginosa* (strains: 24226, 24227, 24228 and 24354)

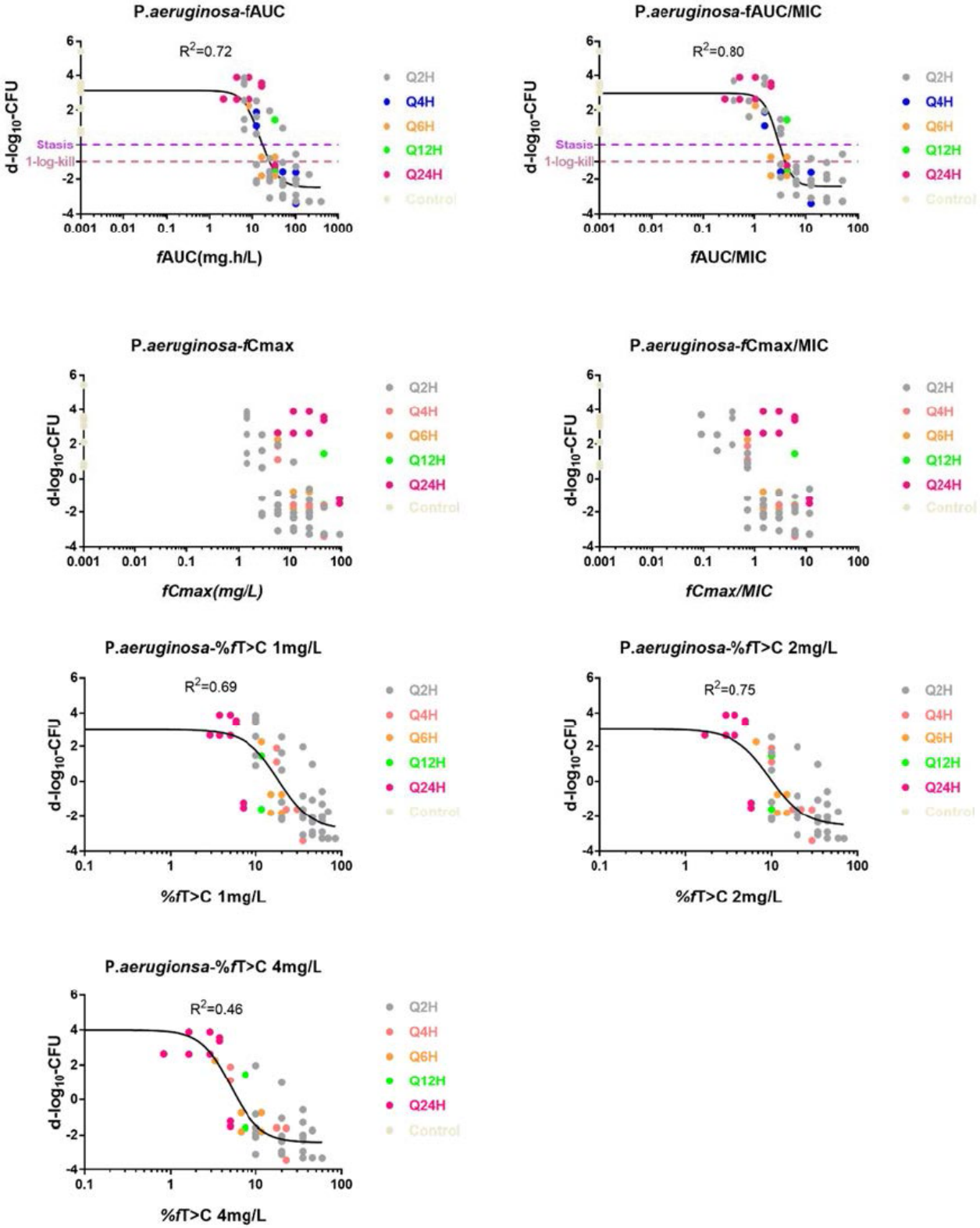
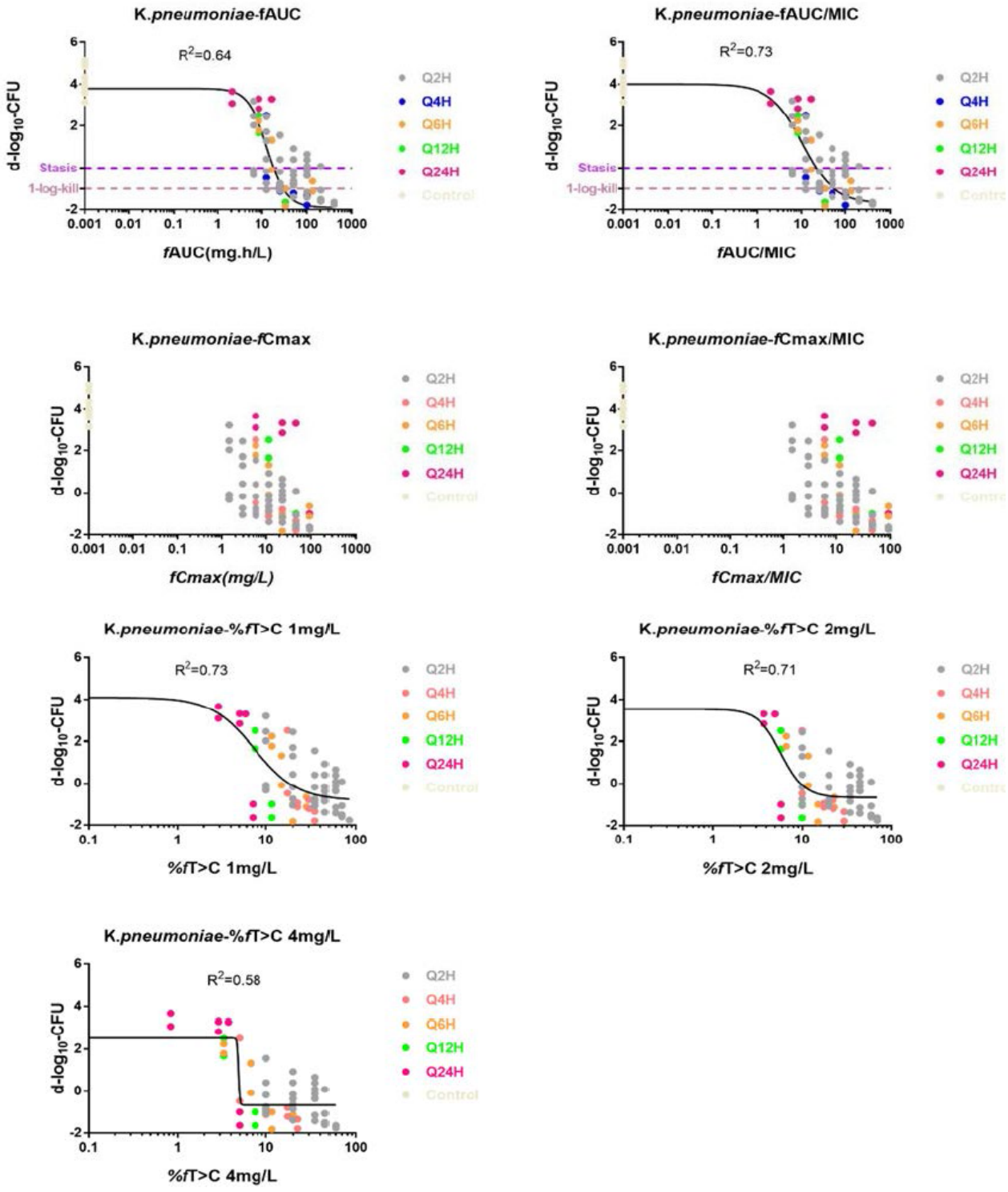


Figure PD3b. PK/PD relationship of REL in the neutropenic mouse thigh infection model at IMI 8 mg/kg and 15.9 mg/kg for *K. pneumoniae* (strains 6339, 6755)



The table below shows the REL AUC for stasis (total and free fraction) and the PK/PD index *f*AUC/MIC for REL to achieve a static effect in the different experiments. It should be noted that there is a typographical error in the table. The strain 24266 should be 24226. The two higher *f*AUC/MIC targets to achieve stasis for this

strain (8.2 and 10.6) was achieved when doses of IMI were 4- to 8-fold lower than the humanised dose. Therefore, there seem to be a need for more REL to achieve stasis when lower doses of IMI are evaluated. The internal MIC-value missing in the table for strain 6755 was ≤1 mg/L.

Table PD7. PK/PD targets using REL AUC normalized by MIC for the thigh infection model

Genus/Species	Strain	Merck Imipenem/ REL MIC (µg/mL)[a]	PD017 Imipenem/ REL MIC (µg/mL)[a, b]	REL AUC for Stasis (µM•h)	REL Free AUC for Stasis (mg•h/L)	REL Total AUC for Stasis (mg•h/L)	REL Free AUC (mg•h/L)/ MIC (µg/mL)[c]
K. pneumoniae	6339	0.25	0.25	18.1	6.3	8.1	25.2
P. aeruginosa	24266	4	0.5	94.2	32.8	42.1	8.2
P. aeruginosa	24266	4	0.5	121.1	42.2	54.1	10.6
P. aeruginosa	24266	4	0.5	35.9	12.5	16.0	3.1
P. aeruginosa	24354	16	2	129.7	45.2	57.9	2.8
P. aeruginosa	24227	2	0.25	18.4	6.4	8.2	3.2
P. aeruginosa	24228	8	0.5	78.1	27.2	34.9	3.4
K. pneumoniae	6755	NA	0.125	115.7	40.3	51.7	NC
K. pneumoniae	6755	NA	0.125	60.9	21.2	27.2	NC

a MIC values are based on in vitro studies where imipenem/REL was used. As cilastatin does not possess intrinsic antibacterial activity, it is not included in these in vitro studies.

b Based on Study PD017 and Mavridou et al, 2015 [Ref. 4.3: 04M693].

c Based on Merck internal data.

Note calculations based on molecular weight of 348.38 gram per mole.

AUC = area under the concentration-time curve; h = hour(s); L = liter; mg = milligram; µg/mL = microgram per milliliter; MIC = minimum inhibitory concentration; µM = micromolar; NA = not available; NC = not calculated

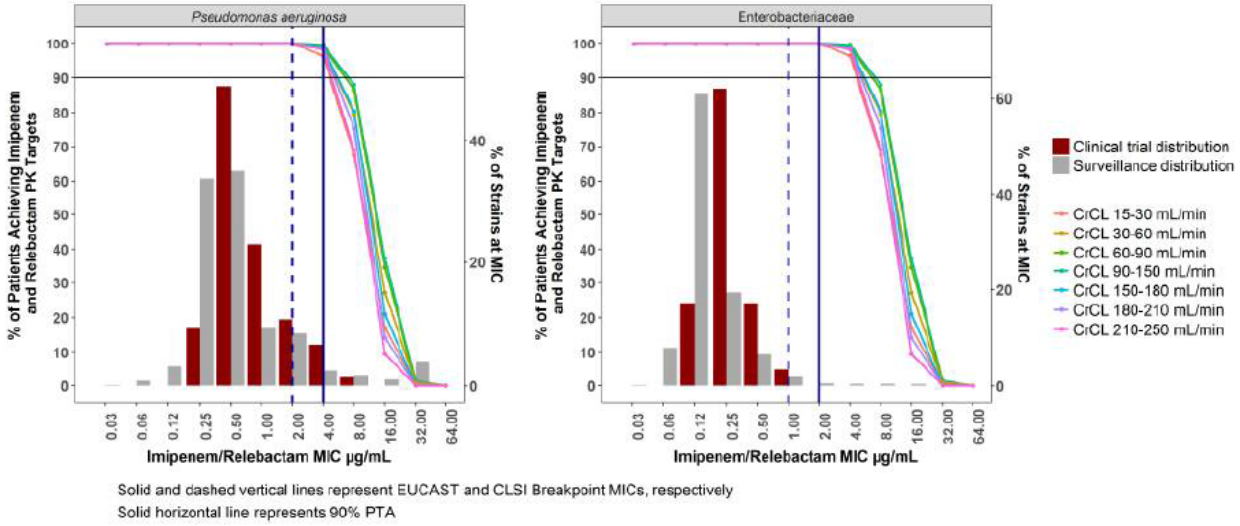
Summary of support for dose selection

The PDTs derived from neutropenic mouse thigh model studies for REL (*f*AUC$_{0\text{-}24hr}$/MIC≥5.2; which was the mean of the stasis targets from all *P. aeruginosa* experiments found in table PD7) and the IMI PK target of 6.5% *f*T>MIC derived from HFIM studies were initially used to assess probability of joint target attainment based on popPK modelling with integrated Phase 1, 2 and 3 data. Based on these PTA simulations, the clinical dose of 500-mg IMI co-administered with 250-mg REL every 6 hours infused over 30 minutes will be satisfactory (PTA >90%) for the treatment of infections in subjects with different renal function categories up to an MIC of 4 mg/L (table PD8 and figure PD4).

Table PD8. Percentage of patients achieving 6.5% of fT>MIC for IMI and *f*AUC/MIC=5.2 for REL at steady state

CrCL	Percentage of Patients Achieving 6.5% of *f*T>MIC for Imipenem and *f*AUC/MIC=5.2 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	98.6	81.9	35.0	2.0	0
15 - 30 mL/min	100	100	100	100	100	100	100	96.3	67.6	17.0	0.4	0
30 - 60 mL/min	100	100	100	100	100	100	100	98.3	79.5	27.1	1.0	0
60 - 90 mL/min	100	100	100	100	100	100	100	99.1	86.5	34.4	1.0	0
90 - 150 mL/min	100	100	100	100	100	100	100	99.6	88.0	37.0	1.4	0
150 - 180 mL/min	100	100	100	100	100	100	100	98.9	80.4	20.9	0.2	0
180 - 210 mL/min	100	100	100	100	100	100	100	98.5	75.5	14.2	0.1	0
210 - 250 mL/min	100	100	100	100	100	100	100	98.2	69.0	9.4	0.1	0

Figure PD4. Percentage of patients achieving 6.5% of fT>MIC for IMI and fAUC/MIC=5.2 for REL at steady state with *P. aeruginosa* and Enterobacteriaceae MIC distributions amongst isolates relevant of proposed indication from clinical phase 2/3 and surveillance data



However, the 6.5% *f*T>MIC target for IMI to achieve 2-$\log_{10}$ CFU reduction when combined with REL derived from the hollow-fibre model experiments is much lower than the well-established targets of 40% *f*T>MIC for IMI alone to achieve 2-$\log_{10}$ CFU reduction. Moreover, the finding of this lower target has not been confirmed in the neutropenic thigh model. Therefore, at the request of CHMP the Applicant has provided additional PTA simulations at the 40% (and 30%) *f*T>MIC target for IMI and 7.5 *f*AUC/MIC target for REL, corresponding to 2-$\log_{10}$ CFU reduction (based on HFIM data) against *P. aeruginosa*. The target to achieve the 2-$\log_{10}$ CFU reduction for REL in the thigh model against *P. aeruginosa* was similar (7), which is why the 7.5 *f*AUC/MIC REL target chosen is considered acceptable for these analyses (figures and tables below).

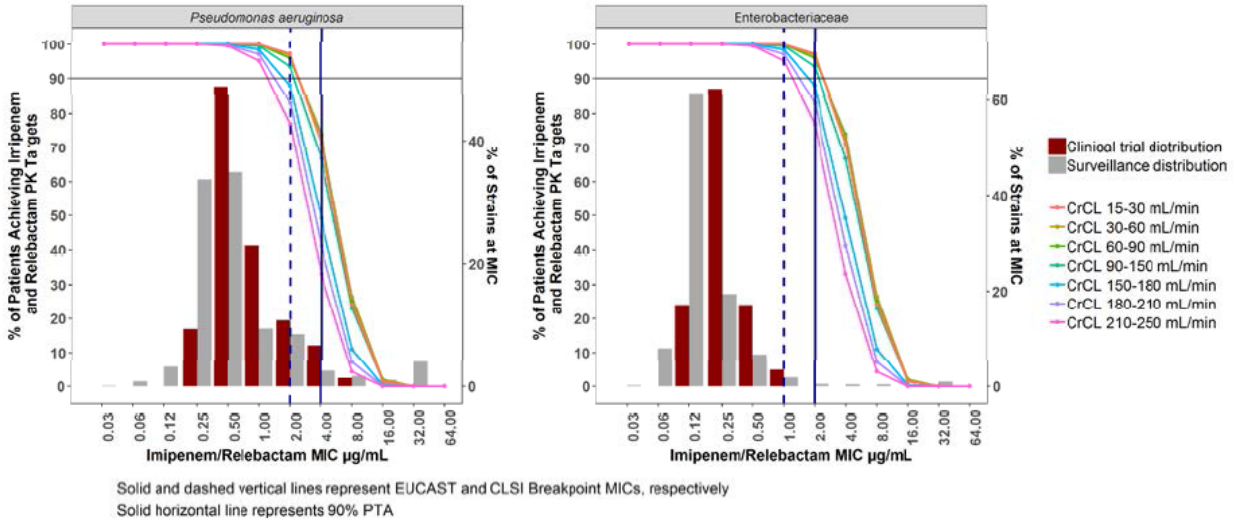
In the PTA simulations using the 30% target for IMI, the proposed doses for IMI and REL are demonstrated to be sufficient to reach >90% PTA up to an MIC of 2 mg/L for subjects in all renal function categories with the lowest PTA (92.5%) for subjects with a creatinine clearance of 210-250 mL/min (data not shown).

When the 40% target for IMI was used in the simulations, which was the target requested by the CHMP, it is shown that the proposed doses for IMI and REL are sufficient to reach >90% PTA up to an MIC of 2 mg/L for subjects in all renal function categories except those with augmented renal clearance (creatinine clearance above 150 mL/min) with the lowest PTA (76.9%) for subjects with a creatinine clearance of 210-250 mL/min. For subjects with augmented renal clearance a PTA above 90% is reached for pathogens up to an MIC of 1 mg/L.

Table PD9. Percentage of patients achieving 40% of fT>MIC for IMI and fAUC/MIC=7.5 for REL at steady state

MIC (mg/L)	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	99.6	90.3	48.4	10.1	0.5	0
15 - 30 mL/min	100	100	100	100	100	100	97.3	71.2	24.2	1.4	0	0
30 - 60 mL/min	100	100	100	100	100	100	96.8	73.3	26.4	1.8	0.1	0
60 - 90 mL/min	100	100	100	100	100	99.9	96.0	74.0	25.5	2.0	0	0
90 - 150 mL/min	100	100	100	100	100	99.5	93.5	66.9	23.0	1.5	0	0
150 - 180 mL/min	100	100	100	100	100	98.4	87.9	49.3	11.0	0.3	0	0
180 - 210 mL/min	100	100	100	100	99.7	97.1	83.1	41.3	7.1	0.1	0	0
210 - 250 mL/min	100	100	100	100	99.5	95.2	76.9	33.1	4.3	0	0	0

Figure PD5. Percentage of patients achieving 40% *f*T>MIC for IMI and *f*AUC/MIC=7.5 for REL with *P. aeruginosa* (left) and Enterobacteriaceae (right) MIC distributions amongst isolates relevant to proposed indication from clinical phase 2/3 and surveillance data



Susceptibility testing breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Organism group	**Minimum Inhibitory Concentrations (mg/L)**	
	Susceptible ≤	**Resistant >**
Enterobacterales (except Morganellaceae)	2	2
Pseudomonas aeruginosa	2	2
Acinetobacter spp.	2	2
Viridans group streptococci	2	2
Anaerobes, gram-positive	2	2
Anaerobes, gram-negative	2	2

Secondary pharmacodynamics

Thorough QTc evaluation

In study P009, a total of 36 healthy adult subjects were included in order to evaluate the impact on the QTc interval of a single dose of 1150 mg REL. The study was a single dose randomized placebo- and positive controlled (moxifloxacin), 3-period, balanced crossover study with a washout period of at least 4 days between dosing and included 36 subjects.

None of the subjects who received 1150 mg REL experienced a QTcP of < 450 msec at any pre-specified time point. Only one subject had a change from baseline of > 30 and < 60 msec, which occurred at 6 hours post dose. This subject experienced a 34 msec change from baseline which was not considered clinically significant and was not associated with any clinical signs/symptoms. The categorical analysis of PR and QRS indicate that MK-7655 had no effect on these parameters, and although the 95% CIs did not include zero at some time points the increases were very small. Analysis of other ECG parameters, including PR and RR intervals, QRS duration, T-wave morphology, presence of U-waves and outlier assessments could not identify any cardiac safety concerns related to administration of a single dose relebactam 1150 mg.

Table PD10. Summary Statistics of QTcF (msec) Change From Baseline by Treatment and Time Point Following the Administration of a Single IV Dose of 1150 mg Relebactam, a Single Oral Dose of 400 mg Moxifloxacin, and a Single IV Dose of Matching Placebo to Relebactam in Healthy Adult Subjects

		QTcF Value (msec)			Change From Baseline (msec)	
Treatment	Time (hr)	N	Mean	95% CI	Mean	95% CI
Placebo	Predose[1]	36	408.94	(403.32, 414.55)		
	0.25	36	406.42	(400.89, 411.94)	-2.52	(-4.22, -0.81)
	0.50	36	405.95	(400.51, 411.40)	-2.98	(-4.38, -1.58)
	1	36	408.45	(402.67, 414.24)	-0.48	(-2.07, 1.11)
	2	36	407.12	(401.52, 412.72)	-1.81	(-3.53, -0.10)
	3	36	408.31	(402.92, 413.71)	-0.62	(-2.78, 1.54)
	4	36	408.21	(402.78, 413.65)	-0.72	(-2.75, 1.30)
	6	36	404.50	(399.68, 409.32)	-4.44	(-7.60, -1.27)
	12	36	403.12	(397.99, 408.25)	-5.81	(-8.73, -2.90)
	24	36	403.06	(398.04, 408.07)	-5.88	(-8.27, -3.49)
MK-7655	Predose[1]	36	408.56	(403.17, 413.96)		
	0.25	36	409.00	(403.69, 414.31)	0.44	(-1.30, 2.17)
	0.50	36	407.79	(402.51, 413.07)	-0.78	(-2.18, 0.63)
	1	36	408.11	(402.46, 413.77)	-0.45	(-2.03, 1.12)
	2	36	407.51	(401.91, 413.11)	-1.06	(-2.79, 0.68)
	3	36	408.35	(403.03, 413.67)	-0.21	(-1.81, 1.38)
	4	36	410.72	(404.59, 416.85)	2.16	(0.11, 4.20)
	6	36	405.48	(400.05, 410.91)	-3.08	(-6.38, 0.21)
	12	36	404.19	(399.49, 408.90)	-4.37	(-7.25, -1.49)
	24	36	404.13	(398.70, 409.56)	-4.44	(-6.47, -2.40)
Moxifloxacin	Predose[1]	36	410.46	(404.81, 416.11)		
	0.25	36	411.72	(405.54, 417.90)	1.26	(-0.50, 3.02)
	0.50	36	413.52	(406.94, 420.10)	3.06	(0.13, 5.99)
	1	36	419.36	(413.20, 425.52)	8.90	(6.31, 11.50)
	2	36	420.06	(414.35, 425.76)	9.60	(7.54, 11.65)
	3	36	422.51	(416.40, 428.62)	12.05	(9.25, 14.84)
	4	36	424.13	(417.92, 430.34)	13.67	(11.09, 16.25)
	6	36	413.68	(408.47, 418.88)	3.22	(-0.57, 7.01)
	12	36	411.13	(405.79, 416.47)	0.67	(-2.76, 4.10)
	24	36	410.90	(405.35, 416.44)	0.44	(-1.29, 2.16)

MK-7655: A single IV dose of 1150 mg MK-7655 (100 mL IV solution for infusion) administered on Day 1.
Moxifloxacin: A single oral dose of 400 mg moxifloxacin administered on Day 1.
Placebo: A single IV dose of placebo (100 mL IV solution for infusion) administered on Day 1.
Non-modal-based means and 95% confidence intervals calculated based on t-distribution.
[1]Average of measurements over 3 predose time points serves as baseline.
CI = Confidence interval; N denotes the number of subjects for each level of treatment with QTcF change-from-baseline value.

Source: P009 Table 14-5

Pharmacodynamic interactions with other medicinal products or substances

In vitro studies have demonstrated no antagonism between IMI/REL and amikacin, azithromycin, aztreonam, colistin, gentamicin, levofloxacin, linezolid, tigecycline, tobramycin, or vancomycin.

Exposure-response for efficacy in the clinical studies

No relationship was observed between drug exposure and response in the Phase 2 and Phase 3 studies.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

As this is a standalone application, and as the approved products containing imipenem+cilastatin (e.g. Tienam) are not centrally approved, comprehensive data is requested for imipenem and cilastatin. At CHMP request, the Applicant has provided an overview of pharmacokinetic properties of imipenem and cilastatin.

The Applicant has presented all bioanalytical reports, which were assessed by CHMP.

The popPK models are important to provide input exposures to the PTA simulations for both imipenem and relebactam. In addition, the models need to capture well the effect of renal impairment to support the dosing recommendations in different degrees of renal dysfunction. Constructing separate models for relebactam and imipenem is considered adequate since there are no signs that concomitant administration of imipenem and

relebactam affect the plasma PK of either drug. It is noted that no popPK model was developed for cilastatin, and it is argued that this agent is only added to avoid degradation of imipenem, and that any significant changes in cilastatin PK will be seen in imipenem pharmacokinetics. This approach is agreed by CHMP.

The most informative covariate on clearance for both imipenem and relebactam was Clcrea, which is expected for renally excreted drugs. An additional effect of weight was detected for imipenem only. It was tested in an exponential fashion with estimated exponent. Estimating both weight and CrCL on clearance may not be optimal since they are correlated. Normally, weight should be included in an allometric fashion, preferably with fixed exponents, to account for the effect of size on clearance. The applicant updated the popPK models for both imipenem and relebactam with bodyweight based allometric scaling with fixed exponents. The parameter estimates are similar to the previous models, and the RSEs are considered reasonable, both for imipenem and for relebactam. Overall, the updated models are similar to the previous models. This show robustness in the estimates and thus the developed models without fixed allometric scaling are accepted and the previously simulated PTAs (with correct targets) are accepted.

No mass balance study with labelled relebactam was performed. This is considered acceptable by CHMP, as most of an administered dose was found unchanged in urine. Relebactam was found to be almost exclusively renally excreted. This was true also for cilastatin. Imipenem was also renally excreted, but to a somewhat lower extent (53-71%). CHMP noted that this is in line with the information in the approved SmPC of Tienam.

Average renal clearance of relebactam was estimated to 135 ml/min. Passive filtration could be estimated to fuxGFR ~0.78x120 ml/min = 94 ml/min. As renal clearance appears to be higher than passive filtration, a role of renal secretion (around 40 ml/min of total clearance 148 ml/min → around 30% of total clearance) is expected. As active secretion is more than 25% of total elimination, the identities of the active transport proteins were investigated. Relebactam was shown to be an *in vitro* substrate of OAT3, OAT4, MATE1 and MATE2K, and these may play a role in the active secretion of relebactam. Only a minor clinical increase in exposure was however observed when the OAT transporters were inhibited with probenecid, in line with the relatively small expected role of active secretion.

The Applicant has performed an acceptable dedicated renal impairment study and results are presented in different groups in relation to absolute creatinine clearance, which is endorsed. As there is a larger effect of renal impairment on relebactam PK than on imipenem PK due to a higher fe, a dose adjustment with the same ratio between the components can never obtain the same exposure in all renal function groups for both entities. A slightly higher exposure to relebactam in patients with renal impairment is probably acceptable to retain sufficient imipenem exposure in all groups. The effect of renal impairment on cilastatin exposure has not been fully addressed in this application, but in the SmPC of Tienam the magnitude of effect of mild, moderate and renal impairment is reported to be in the same range as for relebactam (AUC increase up to 1.6, 1.9 and 5.6-fold). The proposed dose reductions appear to be fully in line with the approved dosing of Tienam and is deemed acceptable by CHMP.

Apart from renally impaired patients, there are no major concerns regarding pharmacokinetic alterations in other special population. No effect of hepatic impairment is expected on the PK of any of the compounds, and thus lack of data is acceptable. As expected for a renally eliminated compound, male subjects had a slightly higher clearance of relebactam than females, and elderly had a somewhat lower clearance than younger subjects in the study. This is in line with an expected difference in absolute renal function. No major effect of weight on clearance is expected except the effect on renal elimination, and thus dose adjustment based on absolute creatinine clearance rather than on body weight is supported. No effect of race is expected, and the limited data available (in particular a PK study in Japanese subjects), did not suggest any effect of race on the PK of neither imipenem nor relebactam.

A standard set of *in vitro* experiments has been performed investigating relebactam as an inhibitor or inducer of CYP enzymes and transporters. No signs of inhibition or induction were observed.

In vitro studies with pooled human liver microsomes were conducted in order to investigate inhibitory potential (direct and time-dependent) towards 7 CYP isoforms, namely: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Experiments in cryopreserved human hepatocytes from 3 donors were conducted to investigate induction potential for CYP3A4, CYP2B6 and CYP1A2. All *in vitro* experiments with CYP enzymes included relebactam concentrations of up to 2 mM (as required by EMA/CHMP guideline on drug interactions).

The transporter inhibition experiments were performed at maximum concentrations somewhat lower than the worst-case concentrations stipulated by the DDI guideline. However, no trends towards concentration-dependent inhibitions were observed within a quite wide concentration range of relebactam between 1 and 500 µM. These experiments are therefore considered acceptable and no further data are requested. Relebactam and imipenem are both renally eliminated, partly by renal secretion. The risk of drug-drug interactions with inhibitors of renal transporters however appears low. The 24% increase in AUC of relebactam observed in the DDI study with probenecid confirms a role, although minor, of OAT-transporters in the secretion of relebactam. The results concerning imipenem are in line with previous knowledge as expressed in the SmPC of Tienam. In Tienam SmPC the effect of probenecid on the PK of cilastatin is also mentioned, informing that probenecid doubled cilastatin plasma levels but did not influence the amount of cilastatin found in urine. Moreover, in Tienam SmPC the effect of probenecid on cilastatin's plasma exposure (2-fold increase) and its half-life (2-times longer) is also described, however Applicant has not quantified/presented cilastatin's exposure from the current *in vivo* experiment with probenecid. CHMP agreed with the Applicant that the PK increases observed for both relebactam and imipenem are modest and are not considered clinically meaningful.

The Applicant was asked by CHMP to perform a literature search and to discuss if there are any new drug-drug interactions of potential relevance for imipenem and/or cilastatin which should be added to the SmPC.

The Applicant has performed search in the "Company's Product Literature Database, a product related database that contains abstracts of published clinical articles on company-owned products" and concluded that there were no new published articles that are providing new relevant information regarding drug-drug interactions involving imipenem and/or cilastatin. CHMP noted the above.

Pharmacodynamics

Mechanism of action

IPM (a carbapenem β-lactam antibacterial agent) and CIL (a renal dehydropeptidase inhibitor that limits the renal metabolism of IMI) are known active substances authorised as FDCs (e.g. Tienam) in EU countries since the 1980s. REL is a novel diazabicyclooctane (DABCO) β-lactamase inhibitor that inhibits a variety of Ambler class A and C but not class B and D β-lactamases. Because IMI is stable to the majority of serine β-lactamases, the most important role of REL in the FDC is the ability to inhibit KPC- and PDC carbapenemases in Enterobacteriaceae and *P. aeruginosa*, respectively. With regards KPC, the dossier is focussed on REL´s ability to restore the susceptibility of IMI in strains expressing the most prevalent KPC subtypes (KPC-2 and KPC-3). Although the number of isolates carrying other KPC subtypes were relatively limited the data provided suggests that REL inhibits also other KPC subtypes.

In vitro

Against a panel of *P. aeruginosa* strains, IMI MIC values shifted downwards to lower concentrations as the concentration of REL increased up to 16 µg/mL. Additional increase of REL concentration above 16 µg/mL added minimal activity. Against strains of Enterobacteriaceae, REL concentrations above 4 µg/mL added little to the activity of IMI. Since the C_{avg} of the clinical REL dose (250 mg q6h) is approximately 4 µg/mL it could be anticipated that a higher dose of REL in the FDC could potentially improve the activity of IMI further, at least against IMI-resistant *P. aeruginosa*.

When IMI and IMI/REL susceptibility were evaluated in large panels of *P. aeruginosa* isolates from the SMART global surveillance program there was a shift downwards in MIC_{90} from 16 mg/L to 4 mg/L. When all IMI-non-susceptible isolates from all sources were pooled (isolates with IMI MICs ≥4 mg/L based on CLSI criteria) it is noted that 75.4% of these isolates were susceptible to IMI/REL based on EUCAST susceptibility testing interpretive criteria for IMI. At an IMI MIC above 32 mg/L very few isolates of *P. aeruginosa* become susceptible when REL is added. The higher the IMI MIC, the more likely it is that the isolates produce metallo β-lactamases (class B) which are not within the inhibitory spectrum of REL.

For Enterobacteriaceae the beneficial effect of adding REL to IMI is especially noted for isolates producing KPC. The IMI MIC_{90} for KPC-producing Enterobacteriaceae (SMART global surveillance study) shifted from ≥32 mg/L to 1 mg/L when REL was added. For non-KPC- but ESBL- or AmpC-producing Enterobacteriaceae only 2 to 4-fold shifts in MIC_{90} were noted. These shifts do not significantly decrease the percentage of resistant isolates as per the EUCAST cut-off for resistance (>4 mg/L) as compared for the effect of REL in KPC-producers because of the inherent stability of IMI to ESBL- and AmpC-enzymes.

Because of the inhibitory spectrum of REL, IMI/REL is not expected to be active against isolates that produce class B β-lactamases and class D carbapenemases. Expression of certain alleles of the class A β-lactamase Guiana extended-spectrum β- lactamase (GES) and overexpression of PDC coupled with loss of imipenem entry porin OprD may confer resistance to imipenem/relebactam in *P. aeruginosa*. The expression of efflux pumps in P. aeruginosa does not affect activity of either imipenem or relebactam. Mechanisms of bacterial resistance that could decrease the antibacterial activity of IMI/REL in Enterobacteriaceae include porin mutations affecting outer membrane permeability.

Based on selection of resistance studies, the Applicant concluded that spontaneous resistance against IMI/REL is anticipated to occur at a very low frequency among *Pseudomonas* and most KPC-expressing *Klebsiella*. It is however clear that at least for some isolates the frequency of spontaneous resistance mutation is not negligible and the risk for selection of resistance during treatment cannot be excluded.

The antibacterial activity and suppression of resistance of IMI and IMI/REL were investigated in various HFIM experiments simulating different doses of IMI and REL against a reasonable number of IMI-resistant *P. aeruginosa* and Enterobacteriaceae isolates.

Against the Enterobacteriaceae isolates IMI/REL doses of 500/250 mg was sufficient to achieve rapid killing and to prevent regrowth. This was also true for the majority of *P. aeruginosa* strains, however against one strain with an IMI/REL MIC of 16 mg/L the IMI/REL dose of 500/125 mg was not efficacious. At 500/250 mg, although a 4-$\log_{10}$ reduction was reached and regrowth was prevented, the killing rate was significantly slower than for other isolates tested. Against one *P. aeruginosa* isolate with an IMI/REL MIC of 4 mg/L regrowth was detected at 48 h despite the highest doses of IMI/REL simulated (1000/500 mg q6h).

These findings suggest that at least for some *P. aeruginosa* isolates the dose of IMI and/or REL would preferably have been higher than the clinical dose chosen to optimise the antibacterial effect and suppression

of resistance. It is noted that the starting inoculum in the HFIM studies were 10^5 to 10^6 CFU/mL. A higher starting inoculum increases the likelihood of including pre-existing mutants. Therefore, the study design may not have been optimised to select for such mutants.

The Applicant has provided support for their conclusion that REL´s activity is best correlated with *f*AUC/MIC based on data obtained using the hollow fibre infection model. The Applicant has clearly focussed their dose-ranging experiments on *P. aeruginosa* and not performed dose-ranging for Enterobacteriaceae but used the clinical dosing regimen in these experiments. It is furthermore clear from the figures that q6h dosing was most frequently used in the experiments also for *P. aeruginosa.* There seems to be a time-dependency of the activity of REL in that the activity increases with more frequent dosing. However, it is unclear whether this correlation would come out stronger than the correlation of REL´s activity to *f*AUC/MIC if the dose-ranging was less focussed on q6h dosing. However, the PK/PD index that best correlated with RELs activity for *P. aeruginosa* based on the data provided was *f*AUC and *f*AUC/MIC (r^2 = 0.71) making it reasonable to claim that *f*AUC/MIC as an index relevant to predict the activity of REL. This was furthermore consistent with the findings in the neutropenic thigh model (see below). The REL *f*AUC/MIC target values associated with stasis, 1-$\log_{10}$ and 2-$\log_{10}$ bacterial load reduction for *P. aeruginosa* in the hollow fibre model were 2.9, 4.8 and 8.2, respectively.

It is accepted that the PK/PD index best descriptive of efficacy for IMI is % *f*T>MIC. The Applicant argues that based on a single HFIM study that the % *f*T>MIC required for 2-log kill of IMI when combined with REL is 6.5% *f*T>MIC instead of the historical target to achieve similar bactericidal effect of at least 40% *f*T>MIC. This was the target considered acceptable by the CHMP in the assessment of the IMI dose in the referral procedure for Tienam (EMA/513740/2011) which led to the current dose recommendations for IMI when used alone. The lower target found could according to the Applicant be due to an overestimation of the IMI/REL MIC with the current method and that the IMI/REL MIC should be treated as a dynamic related to the varying REL plasma concentration. However, the Applicant has not provided any new experimental support of the 6.5% *f*T>MIC target for IMI when combined with REL derived from HFIM studies as requested by the CHMP. If this finding would have been confirmed by repeated HFIM studies and in neutropenic murine thigh model studies in IMI susceptible and non-susceptible isolates it would likely support the use of this lower target in the PTA simulations.

As noted by the original PTA simulations provided by the Applicant and those simulations that use 30% and 40% *f*T>MIC IMI targets, it is the dose of IMI that limits the utility of IMI/REL. A lower IMI target would likely support the possibility to treat pathogens with higher MICs which would be very valuable at least for *P. aeruginosa*. The Applicant´s argues that the model used, and strains tested, should be enough to rely on the lower 6.5% IMI target. However, there is no proof-of-concept that a β-lactam target will be lower when combined with a β-lactamase inhibitor. None of the earlier applicants for BL/BLI combinations has explored this in detail. The lack of confirmation of the lower IMI target and the overall lack of positive controls in HFIM and animal model studies is a weakness of the application but also for the understanding of the effect on the β-lactam target when combined with a β-lactamase inhibitor. The use of historical targets for the β-lactam alone have been considered acceptable in earlier applications for BL/BLI combinations.

It should be noted that because the finding of the 6.5% *f*T>MIC target has not been confirmed, it questions the validity of conclusions drawn for REL achieved in the same *in vitro* system. The issue of using REL targets derived from the HFIM model remains despite similar target values achieved in the HFIM and neutropenic murine thigh models.

In vivo

The *in vivo* efficacy of IMI/REL has been assessed in several murine models of infection.

In the delayed pulmonary infection model a static response to therapy in this model is considered indicative of clinical efficacy (Craig and Andes, 2008). Three sets of experiments were performed with IMI/REL (with different doses of REL) and IMI alone (5 mg/kg q6h) against one IMI-non-susceptible strain of *P. aeruginosa.* A dose of REL of at least 20 mg/kg q6h resulted in a static effect. The plasma exposures of the 20 mg/kg dose of REL were 40.0, 63.3 and 42.0 mg×hour/L, respectively in the three independent studies corresponding to a free drug $AUC_{0\text{-}24\ hr}$/MIC target of 4.0, 6.2 and 4.2, respectively.

Additional experiments using the delayed pulmonary infection model were performed with IMI/REL against nine strains of *P. aeruginosa* and two strains of *K. pneumoniae* resistant to IMI. Stasis was achieved against 8 of 9 isolates of *P. aeruginosa*. The average 24 h plasma exposure to achieve stasis against *P. aeruginosa* was 41.9 mg×hour/L (range 11.1 to 148) which translates to a mean free drug $AUC_{0\text{-}24\ hr}$/MIC target of 4.0 (range 1.0 to 14.6). As some strains were tested several times a relatively high within strain variation of the activity was noted (six-fold). The average 24-hour plasma exposure to achieve stasis against *K. pneumoniae* (41.4 mg×hour/L; range 20.5 to 81.3) was essentially comparable to the exposure needed for stasis against isolates of *P. aeruginosa*. However, due to the lower IMI/REL MICs for the *Klebsiella* strains the free drug $AUC_{0\text{-}24\ hr}$/MIC to achieve stasis was several folds higher (free drug $AUC_{0\text{-}24\ hr}$/MIC 70.5, 64.8 and 128.5, respectively).

The Applicant has provided support for their conclusion that REL´s activity is best correlated with *f*AUC/MIC based on data obtained using the neutropenic mouse thigh model. Graphs for *f*AUC, fC_{max}, $\%fT>C_T$ (using different thresholds), *f*AUC/MIC and fC_{max}/MIC are provided and the dosing interval for REL used for each data-point are displayed by different colours in the graphs as requested. Graphs for the four *P. aeruginosa* and two *K. pneumoniae* strains are presented separately. The Applicant has confirmed that IMI was given every 2 h in combination with different doses of REL and moreover that the control is IMI without the addition of REL.

Clearly, dose-fractionation was only tested for one isolate each of *P. aeruginosa* (pa24228) and *K. pneumoniae* (kp6755). All other isolates were tested at different exposures but only with Q2h dose-regimens. At this dose-regimen the isolates behaved generally similar with increased killing at increasing exposures. The focus on the Q2h dose-regimen is reasonable for this fixed dose combination because the Q2h regimen in mice is corresponding to Q6h human dose-regimens, the dose-regimen used for IMI. With this dose-regimen there was a good correlation between REL´s *f*AUC/MIC and bacterial killing. It is furthermore noted that in addition to the increased killing with increasing exposure there is also a time-dependent component reflected by increased killing when similar total daily doses where given more often. While it may be assumed that dosing REL even more frequently possibly could increase the killing even further it is not reasonable to require that this should be studied further for the reasons stated above.

As discussed above q2h dosing was the most frequently used regimen and the dose-range tested was limited for some of the regimens. In line with the HFIM dose-ranging studies this somewhat hampers the ability to draw reliable conclusions on the PK/PD index best correlated to REL`s activity. However, based on the data at hand the PK/PD index that best correlated with RELs activity for both species was *f*AUC/MIC (for *K. pneumoniae* $\%fT>C_T$ of 1 mg/L correlated similarly well). With the good correlation of REL´s activity to *f*AUC/MIC noted it is reasonable to use this index to explore PK/PD targets.

The Applicant has explained that they used the pooled data to detect the REL target to achieve stasis, 1-$\log_{10}$ and 2-$\log_{10}$ CFU reductions instead of a 90_{th} percentile approach as requested by the CHMP. This was because

it not only allows characterisation of a robust PK/PD relationship but also provides a sufficiently detailed dataset which can cover the entire PK/PD relationship with less uncertainty on the PK/PD curve. The derived stasis,1-log kill and 2-log kill *f*AUC/MIC targets for *P. aeruginosa* were 3.3, 4.3 and 7, respectively. Notably, approximately 10-fold higher *f*AUC/MIC targets are needed for *K. pneumoniae* than *P. aeruginosa* to achieve similar antibacterial effects.

The Applicant has provided additional plots based on neutropenic thigh model data with *P. aeruginosa* and *K. pneumoniae* separately using correction with unpotentiated imipenem MIC-values (data not shown). The PK/PD relationship of *K. pneumoniae* has higher variability when unpotentiated imipenem MIC values are used for the derivation of *f*AUC/MIC as compared to PK/PD relationship plotted using the potentiated IMI MIC.

However, as discussed above, when the *f*AUC corrected by the potentiated MIC is used as PK/PD index there is a disconnect between species with regards the PK/PD target (PDT), with lower PDTs for *P. aeruginosa* than for *K. pneumoniae* to achieve a similar antibacterial effect. This disconnect is also seen when unpotentiated MICs are used for the derivation of *f*AUC/MIC. Again, this questions the conclusion that the *f*AUC/MIC is the best PK/PD index. Although the correlation within each species is somewhat stronger for *f*AUC/MIC than for *f*AUC alone the use of *f*AUC corrected by the MIC creates a 10-fold difference in PDTs between *P. aeruginosa* and *K. pneumoniae*. When looking at *f*AUCs without correction of MICs there seem to be relatively similar exposures needed between species for similar bacterial killing (e.g. an exposure of approximately 30 mg*h/L are needed to achieve 1-log kill for the *P. aeruginosa* AND *K. pneumoniae* isolates; see figure PD3a and 3b).

Even though *f*AUC possibly could be the better PK/PD index to derive PDTs, when considering different species, this issue is not further pursued. The Applicant´s use of the 2 $\log_{10}$ kill *f*AUC/MIC targets for *P. aeruginosa* in the PTA simulations and justification provided in the former round of assessment that the REL dose in combination with IMI is expected to be sufficient also against infections caused by Enterobacteriaceae is considered acceptable.

Dose selection and probability of target attainment

The PDTs derived from neutropenic mouse thigh model studies for REL (*f*$AUC_{0\text{-}24hr}$/MIC≥5.2; which was the mean of the stasis targets from all *P. aeruginosa* experiments found in table PD7) and the IMI PK target of 6.5% *f*T>MIC derived from HFIM studies were initially used to assess probability of joint target attainment based on popPK modelling with integrated Phase 1, 2 and 3 data. Based on these PTA simulations, the clinical dose of 500-mg IMI co-administered with 250-mg REL every 6 hours infused over 30 minutes will be satisfactory (PTA >90%) for the treatment of infections in subjects with different renal function categories up to an MIC of 4 mg/L

However, the 6.5% *f*T>MIC target for IMI to achieve 2-$\log_{10}$ CFU reduction when combined with REL derived from the hollow-fibre model experiments is much lower than the well-established targets of 40% *f*T>MIC for IMI alone to achieve 2-$\log_{10}$ CFU reduction. Moreover, the finding of this lower target has not been confirmed in the neutropenic thigh model. Therefore, at the request of CHMP the Applicant has provided additional PTA simulations at the 40% (and 30%) *f*T>MIC target for IMI and 7.5 *f*AUC/MIC target for REL, corresponding to 2-$\log_{10}$ CFU reduction (based on HFIM data) against *P. aeruginosa*. The target to achieve the 2-$\log_{10}$ CFU reduction for REL in the thigh model against *P. aeruginosa* was similar (7) why the 7.5 *f*AUC/MIC REL target chosen is considered acceptable for these analyses.

When the 40% target for imipenem was used in the simulations, which was the target requested by the CHMP, it is shown that the proposed doses for IMI and REL are sufficient to reach >90% PTA up to an MIC of 2 mg/L for subjects in all renal function categories except those with augmented renal clearance (creatinine clearance above 150 mL/min) with the lowest PTA (76.9%) for subjects with a creatinine clearance of 210-

250 mL/min. For subjects with augmented renal clearance a PTA above 90% is reached for pathogens up to an MIC of 1 mg/L.

Clearly it is the dose of imipenem in the FDC, which is half of the highest dose recommended for authorised imipenem products, that limits the utility of the FDC and that the choice of the 500 mg q6h IMI dose could be questioned. However, taking into account what is recommended in the product information for EU authorised products containing imipenem without the addition of REL and EUCAST recommended breakpoints for imipenem alone, an imipenem dose of 500 mg q6h (or 1 g q8h) is considered adequate with the exception of treatment of very severe infections (exemplified in the EU SmPCs for IMI products alone with neutropenic patients with fever) and for the treatment of less susceptible bacterial species (such as *P. aeruginosa*). In such situations 1000 mg IMI q6h should be used. As an IMI/REL susceptibility breakpoint of 2 mg/L is recommended for *P. aeruginosa* rather than 4 mg/L as recommended for IMI alone, for which 1000 mg q6h would be needed, the dose of IMI/REL is acceptable for the treatment of *P. aeruginosa* up to this lower breakpoint. However, the dose is not considered sufficient to reach the CHMP recommended IMI target of 40% fT>MIC for subjects with ARC as shown by the PTA simulations above. Therefore, an IMI dose of 500 mg q6h in combination with REL is considered acceptable provided that the message that the 500 mg q6h IMI dose may not be sufficient for patients with ARC is conveyed in the SmPC. Moreover, CHMP asked that a similar wording as in the SmPC for products with IMI alone with regards dosing in neutropenic patients and those with very severe infections is included in the IMI/REL´s product information.

The Applicant has provided the following justification for the use of REL´s PK/PD target for *P. aeruginosa* also for the Enterobacteriaceae in the PTA analyses: The effect of REL on the susceptibility to IMI of KPC-producing Enterobacteriaceae is more pronounced than the effect on IMI non-susceptible *P. aeruginosa*. It can be noted by the surveillance data provided that the addition of 4 mg/L of REL to IMI shifts the MIC-distributions more to the left for Enterobacteriaceae than for *P. aeruginosa* (with a factor of 32-64 and 2-8, respectively). Consequently, it is agreed that REL PK/PD targets for *P. aeruginosa* can be used also for Enterobacteriaceae. Additional PTA simulations with separate target values for Enterobacteriaceae are not considered necessary, since the lower potentiated MIC's compared to *P. aeruginosa* will allow for target attainment notwithstanding the higher fAUC/MIC ratios associated with e.g. 1 log kill (notably, when AUC was not adjusted for potentiated MIC, the relation between exposure and log kill was roughly similar for Enterobacteriaceae and *P. aeruginosa)*.

According to the Applicant this is further supported by the overlay of the E_{max} model fit to *P. aeruginosa* HFIM data with the Enterobacteriaceae HFIM data, which shows that the PK/PD target values at stasis, 1-log and 2-log kill for Enterobacteriaceae are expected to be less than that for *P. aeruginosa*. Again, it should be noted that the HFIM studies are not considered reliable for inferences, since the findings on IMI PK/PD are deviant from expectation and have not been appropriately replicated with a positive control. Interestingly, as discussed above this conclusion conflicts with the findings in the neutropenic thigh model in which approximately 10-fold higher *f*AUC/MIC targets are needed for *K. pneumoniae* than *P. aeruginosa* to achieve similar antibacterial effects. In fact, this finding is not compatible with the concept of correcting the *f*AUC with the MIC (both the potentiated and unpotentiated MIC) as this creates a difference of PDTs across species. The use of the potentiated IMI/REL MIC in the PTA simulations is acceptable because of the similar ratio of the unpotentiated to the potentiated MIC for the strains tested.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

The characterisation of relebactam pharmacokinetics is acceptable.

Pharmacodynamics

As this application relies on a limited clinical programme that does not independently demonstrate the efficacy of imipenem-cilastatin-relebactam, the clinical pharmacology programme, including non-clinical PK/PD analyses and PTA simulations using clinical PK data, is pivotal to the application.

Based on the data provided and despite the weaknesses noted including the lack of positive controls in the non-clinical studies it is considered that the clinical dose of imipenem-cilastatin-relebactam 500/500/250 mg q6h has been acceptably justified provided updates of the SmPC to convey the uncertainties with regards the adequacy of the dose for the treatment of patients with augmented renal clearance, very severe infections and subjects with concurrent neutropenia.

2.5. Clinical efficacy

Table E1. Summary of designs for phase 2 and phase 3 clinical studies

Characteristic	Phase 2 Trials		Phase 3 Trial
	PN003	PN004	PN013
Indication	cUTI	cIAI	cUTI, cIAI, and HABP/VABP
Design	Randomized, double-blind, global, multicenter, comparative		Randomized, double-blind, global, multicenter, comparative
Susceptibility of Baseline Causative Pathogen(s)	Empiric treatment; no specific susceptibility requirements for trial entry		Treatment Groups 1 and 2: Imipenem-nonsusceptible; colistin- and imipenem/REL-susceptible Treatment Group 3: Imipenem- and colistin-nonsusceptible; imipenem/REL-susceptible
Investigational Treatment	Treatment Group 1: IMI 500 mg + REL 250 mg[a] Treatment Group 2: IMI 500 mg + REL 125 mg[a]		Treatment Group 1 (double-blind)[b]: IMI/REL (500 mg/250 mg)[c,d] Treatment Group 3 (open-label)[b]: IMI/REL (500 mg/250 mg)[c]
Comparator	Treatment Group 3: IMI 500 mg + Placebo[a]		Treatment Group 2 (double-blind)[b]: Colistin (as CMS 150 mg CBA)[e] + IMI
Frequency and Duration of IV Trial Treatment	Every 6 hours for 4 to 14 days		IMI/REL: Every 6 hours CMS: Every 12 hours Duration: 5 (cUTI or cIAI) or 7 (HABP/VABP) to 21 days[f]
Dose Adjustments	Dose adjustments for renal impairment and weight		Dose adjustments for renal impairment
Subject Population	Hospitalized adults (≥18 years of age) with cUTI	Hospitalized adults (≥18 years of age) with cIAI	Hospitalized adults (≥18 years of age) with cUTI, cIAI, or HABP/VABP as a primary infection site Susceptibility of causative baseline pathogen had to meet criteria above
Planned Enrollment	Approx. 300 subjects with a 1:1:1 randomization ratio	Approx. 351 subjects with a 1:1:1 randomization ratio	Treatment Groups 1 and 2: Approx. 54 subjects with a 2:1 randomization ratio Treatment Group 3: 5 to 10 subjects
Stratification of Enrollment	None	Enrollment stratified by disease severity (APACHE II scores of ≤15, >15). Subjects with an APACHE II score above 30 at screening were excluded.	Enrollment stratified by type of infection (cUTI, cIAI, or HABP/VABP as primary infection site); approx. 18 subjects with each infection type were initially planned to be enrolled, for 15 evaluable subjects with each infection type

APACHE II = Acute Physiology and Chronic Health Evaluation II; CBA = colistin base activity (300 mg CBA corresponds to approx. 720 mg CMS or approx. 9 million IU); cIAI = complicated intra-abdominal infection; CMS = colistin (in the form of colistimethate sodium); cUTI = complicated urinary tract infection; HABP/VABP = hospital-acquired or ventilator-associated bacterial pneumonia; IMI = imipenem/cilastatin; IU = international units; IV = intravenous; REL = relebactam (MK-7655)

[a] IMI and REL were obtained from separate vials and co-infused with separate infusion bags/syringes through a single cannula. Subjects in Treatment Group 3 received placebo for REL to maintain blinding.

[b] Treatment Groups 1 and 2 were randomized; Treatment Group 3 was nonrandomized.

[c] Each dose of IMI/REL was obtained from a single vial as a FDC containing IMI (imipenem/cilastatin 500 mg) and REL 250 mg.

[d] Subjects in Treatment Group 1 received placebo for CMS every 12 hours to maintain blinding.

[e] If a subject received a loading dose of ≥200 mg CBA (~470 mg CMS or ~5.9 million IU) prior to trial entry, the subject began maintenance doses (75 – 150 mg CBA, depending on renal function) upon initiation of IV trial treatment. If a subject had not previously received a loading dose, the subject received a loading dose of 300 mg CBA upon initiation of IV trial treatment, followed by maintenance doses (75 – 150 mg CBA, depending on renal function).

[f] Duration of IV trial treatment longer than 21 days had to be approved by the Sponsor.

2.5.1. Main study

PN013

This was a phase 3, randomised, double blind, active-controlled, multicentre study of IMI/REL compared with colistin (in the form of colistimethate sodium [CMS]) plus IMI (treatment group 2) in adult subjects with cUTI, cIAI or HAP/VAP caused by imipenem-nonsusceptible gram-negative organisms. Randomisation was stratified by infection type.

In addition to the randomised subjects, eligible subjects could also be enrolled into a third non-randomised, open-label treatment group (treatment group 3) to receive IMI/REL.

Methods

Study Participants

Key inclusion criteria included the following:

- Subject was ≥18 years of age at screening
- Adults (≥18 years of age) who required hospitalization and treatment with IV antibiotic therapy for a new, persistent, or progressing bacterial infection with at least 1 of the following primary infection types:
    - HAP or VAP
    - cIAI
    - cUTI
- Culture of specimen obtained from primary infection site within 1 week of trial entry indicated the isolate met the following criteria:
    - Treatment Groups 1 and 2: Bacterial, gram-negative, imipenem non-susceptible, and imipenem/REL- and colistin-susceptible.
    - Treatment Group 3: Bacterial, gram-negative, imipenem non-susceptible, colistin non-susceptible, and imipenem/REL-susceptible.

Key exclusion criteria included the following:

- Subject had an APACHE II score >30 at Screening.
- Subject had an estimated or actual CrCl of less than 15 mL/min or was undergoing haemodialysis or peritoneal dialysis at the time of enrolment.
- Subject was anticipated to be treated with concomitant systemic antimicrobial agents with known coverage of gram-negative bacteria of interest (i.e., Enterobacteriaceae, Pseudomonas spp. and gram-negative anaerobic bacilli).
- Treatment Group 1 and 2 only: Subject received treatment with any form of systemic colistin for >24 hours within the 72 hours immediately prior to initiation of trial treatment.

Treatments

Patients in treatment groups 1 and 2 were randomised to:

- IMI/REL 500/250 mg q6h + colistin placebo, OR
- Colistin as CMS (colistimethate sodium) with a loading dose of 300 mg CBA (colistin base activity) followed by a maintenance dose of 150 CBA after 12 h and repeated q12h + IMI 500 mg q6h.

The dose of IMI/REL and colistin were reduced in patients with renal impairment. For cUTI and cIAI the treatment durations were 5 to 21 days and for HAP/VAP 7 to 21 days. 300 mg CBA corresponds to ~720 mg CMS or 9 million IU.

Patients in treatment group 3 received IMI/REL 500/250 mg q6h only.

Objectives

Primary objective:

1. To estimate the proportion of subjects with favourable overall response to IMI/REL (Treatment Group 1 only) and to CMS + IMI (Treatment Group 2). The overall response was estimated based on the following: (a) survival (based upon all-cause mortality) through Day 28 post-randomization in subjects with HAP/VAP, (b) clinical response at Day 28 post-randomization for subjects with cIAI, and (c) the composite clinical and microbiological response at the Early Follow-up Visit (EFU Visit; Day 5 to 9 following end of therapy [EOT]) for subjects with cUTI.

Key secondary objectives:
1. To estimate the proportion of subjects with a favourable clinical response to IMI/REL (Treatment Group 1 only) and CMS + IMI (Treatment Group 2) at Day 28 post-randomization.
2. To estimate the incidence of all-cause mortality through Day 28 post randomization in Treatment Group 1 (IMI/REL) and in Treatment Group 2 (CMS + IMI).
3. To estimate the proportion of subjects who experience treatment-emergent nephrotoxicity in Treatment Group 1 (IMI/REL) and in Treatment Group 2 (CMS + IMI).

Additional objective
Additional analyses were planned prior to unblinding and locking the clinical database of which the following alternate definition of favourable overall response was supposed to meet CHMP expectations for the primary objective:
1. To estimate the proportion of subjects with favourable overall response to IMI/REL (Treatment Group 1 only) and to CMS + IMI (Treatment Group 2). The overall response was estimated based on the following: (a) clinical response at EFU for HAP/VAP and cIAI and microbiological response at EFU for subjects with cUTI.

Outcomes/endpoints

Primary endpoint
1. The proportion of subjects with a favourable overall response as assessed for each of the 3 infection types. Defined as follows:
- HABP/VABP: survival at Day 28
- cIAI: sustained cure or cure at Day 28
- cUTI: at EFU
    - Clinical response: sustained cure or cure, and
    - Microbiological response: sustained eradication

Secondary endpoints
1. The proportion of subjects with a favourable clinical response at 28 days following initiation of IV trial treatment.
2. The incidence of all-cause mortality within 28 days after initiation of trial treatment.

Additional endpoint
To meet CHMP expectations for the primary endpoint the following endpoint was added before database lock and unblinding:

1. The proportion of subjects with a favourable overall response at EFU as assessed for each of the 3 infection types. Defined as follows:
• HAP/VAP and cIAI: clinical cure
• cUTI: microbiological eradication

Randomisation and blinding (masking)

An interactive voice response system / integrated web response system (IVRS/IWRS) was used for randomisation. Subjects were assigned randomly in a 2:1 ratio to IMI/REL + placebo to CMS or CMS + IMI, respectively. Randomisation was stratified according to infection types.

Statistical methods

The study was planned to randomise approximately 54 subjects in a 2:1 ratio into 2 treatment groups in order to obtain a minimum of 45 subjects who met the criteria for inclusion in the microbiological modified intent-to-treat (mMITT) population. Another 5 to 10 subjects with imipenem-nonsusceptible and colistin-nonsusceptible bacterial infection was planned to be enrolled into a third open-label treatment group. The sample sizes planned for the study arose from logistic feasibility and were not driven by statistical considerations.

No formal statistical testing was performed for the efficacy endpoints. Within group 95% confidence intervals (CIs) for efficacy endpoints were calculated using the Agresti & Coull method. In addition, between-group 90% CIs for the primary and key secondary endpoints were calculated using the stratified Miettinen and Nurminen method, an unconditional, asymptotic method. The between-group estimates were stratified by infection type, where appropriate.

For the primary endpoint evaluation in the mMITT population and for secondary and exploratory endpoints, any subject missing an evaluation for a specific endpoint at any particular visit was considered a "failure" for that endpoint.

Analysis populations

The microbiological modified Intention to Treat (mMITT) population (all randomised subjects who receive at least one dose of IV study therapy and who have at least 1 confirmed imipenem-nonsusceptible, colistin-susceptible, and imipenem/REL-susceptible gram-negative baseline bacterial pathogen) was the primary population for efficacy analyses.

The per-protocol (PP) population will serve as the secondary population for the primary efficacy endpoint. The PP population is a subset of the mMITT population who also meet the following criteria:

1. Meet important diagnostic criteria for entry into the study
2. Have no significant deviation from the protocol that could impact the assessment of efficacy
3. Receive the minimum duration of IV study therapy

In support of evaluation efficacy assessments include evaluation of clinical response. The clinical response was categorised as favourable or unfavourable. To be considered a favourable clinical response at the EFU and Day 28 post-randomisation visit the subject should be categorised as being cured or having sustained cure (prior visit considered cured). A clinical response of cure was only relevant at EFU for subjects with a

response of improved at EOT. The definition of cure included that all pretherapy signs and symptoms had resolved and that no additional antibiotic therapy was required and for cIAI that no unplanned surgical procedures or drainage procedures have been performed.

Subjects with cUTI were evaluated for microbiological response and categorised as favourable or unfavourable. A favourable overall microbiological response at the EFU visit requires "sustained eradication" (defined as a urine culture taken at the EFU visit still shows eradication of the uropathogen (i.e., $\geq 10^5$ CFU/mL is reduced to $<10^4$ CFU/mL) found at study entry of all baseline pathogens).

Results

Participant flow

Fifty-four subjects were screened, and 50 subjects were enrolled in PN013 (47 in the randomized treatment groups [Treatment Groups 1 and 2] and 3 in the open-label treatment group [Treatment Group 3]). A higher percentage of subjects in Treatment Group 1 compared with Treatment Group 2 completed trial treatment (87.1% versus 68.8%) and completed the entire trial (87.1% versus 68.8%). This was due primarily to a lower percentage of subjects in Treatment Group 1 compared with Treatment Group 2 who discontinued trial treatment due to an AE (0/31 versus 3/16 [18.8%]) and who discontinued the trial due to death (1/31 [3.2%] versus 3/16 [18.8%]).

In Treatment Groups 1 and 2, 23 (48.9%) subjects were enrolled with cUTI, 8 (17.0%) subjects were enrolled with cIAI, and 16 (34.0%) subjects were enrolled with HAP/VAP. Fewer subjects with cIAI were enrolled than the 18 that were planned for each infection site. This was because fewer bacterial isolates that were evaluated during pre-screening were from cIAI sources than from cUTI and HAP/VAP sources.

In Treatment Group 3, no subjects were enrolled with cUTI, 2 subjects were enrolled with cIAI, and 1 subject was enrolled with HAP/VAP.

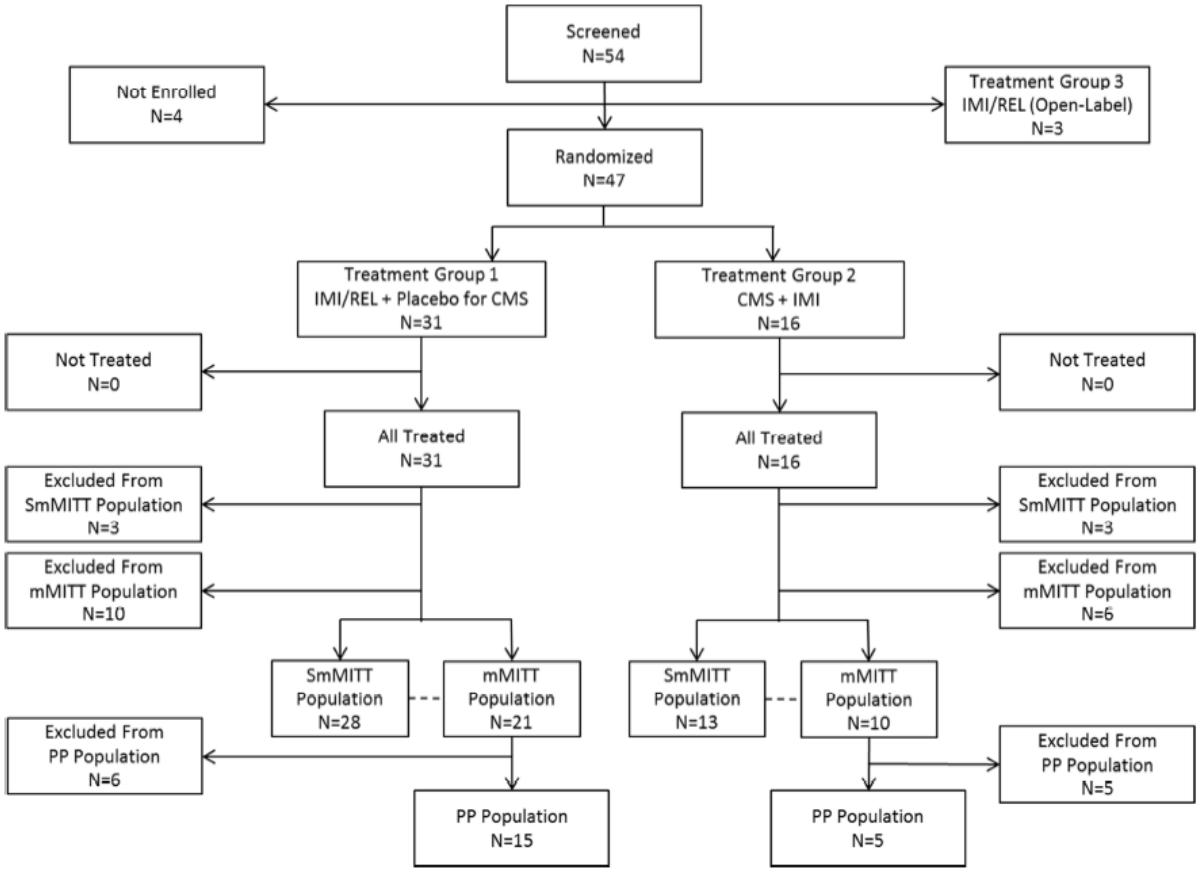
Table E2. Disposition of subjects

	Randomized Treatment Groups						Open-label Treatment Group		Total	
	Treatment Group 1: IMI/REL + Placebo for CMS		Treatment Group 2: CMS + IMI		Total for Randomized Treatment Groups		Treatment Group 3: IMI/REL			
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not enrolled									4	
Subjects in population	31		16		47		3		50	
Trial Disposition										
Completed	27	(87.1)	11	(68.8)	38	(80.9)	1	(33.3)	39	(78.0)
Discontinued	4	(12.9)	5	(31.3)	9	(19.1)	2	(66.7)	11	(22.0)
Adverse Event	0	(0.0)	1	(6.3)	1	(2.1)	1	(33.3)	2	(4.0)
Death	1	(3.2)	3	(18.8)	4	(8.5)	1	(33.3)	5	(10.0)
Lost To Follow-Up	1	(3.2)	1	(6.3)	2	(4.3)	0	(0.0)	2	(4.0)
Physician Decision	1	(3.2)	0	(0.0)	1	(2.1)	0	(0.0)	1	(2.0)
Withdrawal By Subject	1	(3.2)	0	(0.0)	1	(2.1)	0	(0.0)	1	(2.0)
Subject Study Medication Disposition										
Completed	27	(87.1)	11	(68.8)	38	(80.9)	1	(33.3)	39	(78.0)
Discontinued	4	(12.9)	5	(31.3)	9	(19.1)	2	(66.7)	11	(22.0)
Adverse Event	0	(0.0)	3	(18.8)	3	(6.4)	1	(33.3)	4	(8.0)
Death	0	(0.0)	1	(6.3)	1	(2.1)	1	(33.3)	2	(4.0)
Physician Decision	2	(6.5)	1	(6.3)	3	(6.4)	0	(0.0)	3	(6.0)
Treatment Failure	1	(3.2)	0	(0.0)	1	(2.1)	0	(0.0)	1	(2.0)
Withdrawal By Subject	1	(3.2)	0	(0.0)	1	(2.1)	0	(0.0)	1	(2.0)

IMI = imipenem/cilastatin; REL = relebactam; CMS = colistimethate sodium.

Source: [P013MK7655A: adam-adsl]

Figure E1. Study analysis populations



Abbreviations: CMS = colistimethate sodium; IMI = imipenem/cilastatin; mMITT = Microbiological Modified Intent-To-Treat; PP = Per Protocol; REL = relebactam; SmMITT = Supplemental Microbiological Modified Intent-To-Treat.

Among the 16 subjects in Treatment Groups 1 and 2 who were excluded from the mMITT population, 13 subjects were excluded because the pathogens isolated from their infection-site culture did not meet protocol-specified susceptibility criteria based on central laboratory interpretation. For the remaining 3 subjects, the qualifying culture was collected more than 1 week prior to entry. Most common additional reasons for exclusion from the PP population were concomitant antibacterials violation (5 subjects) and protocol-specified infection diagnosis criteria not met (3 subjects).

Compliance and exposure to study drug

Treatment compliance was high in both treatment groups. Moreover, the mean (11.4 and 10.8 days), median (12.5 and 9.8 days) and range (2 to 18 and 2 to 20 days) for duration of exposure to study treatment was similar in treatment group 1 and 2.

Prior and concomitant exposure to other antibiotics

Most subjects in the mMITT population reported prior anti-infective use (83.9% of all subjects) and concomitant (i.e., during IV therapy through end of trial) anti-infective use (71.0% of all subjects). The most commonly reported prior and concomitant anti-infectives were in the antibacterials for systemic use medication class. Treatment Groups 1 and 2 were generally comparable with respect to the incidence and types of prior anti-infective use, with 2 exceptions. Meropenem was used prior to trial treatment by a higher

percentage of subjects in Treatment Group 1 (8 [38.1%] subjects) than in Treatment Group 2 (1 [10.0%] subject), and sulfamethoxazole (+) trimethoprim was used concomitantly by a higher percentage of subjects in Treatment Group 2 (3 [30.0%] subjects) than in Treatment Group 1 (0 subjects).

Baseline data

The demographics and baseline characteristics are shown in the table below.

Table E3. Demographic and subject characteristics of treatment groups 1 and 2 (mMITT population)

North America	0	(0.0)	1	(10.0)	1	(3.2)
Ethnicity						
Hispanic or Latino	3	(14.3)	2	(20.0)	5	(16.1)
Not Hispanic or Latino	18	(85.7)	8	(80.0)	26	(83.9)
APACHE II Score						
APACHE II Score ≤ 15	14	(66.7)	8	(80.0)	22	(71.0)
APACHE II Score > 15	7	(33.3)	2	(20.0)	9	(29.0)
Stratum						
HABP/VABP	8	(38.1)	3	(30.0)	11	(35.5)
cIAI	2	(9.5)	2	(20.0)	4	(12.9)
cUTI	11	(52.4)	5	(50.0)	16	(51.6)
Primary Diagnosis						
HABP	1	(4.8)	1	(10.0)	2	(6.5)
VABP	7	(33.3)	2	(20.0)	9	(29.0)
cIAI	2	(9.5)	2	(20.0)	4	(12.9)
cUTI with UT abnormalities	5	(23.8)	3	(30.0)	8	(25.8)
cUTI, acute pyelonephritis	6	(28.6)	2	(20.0)	8	(25.8)
Secondary Diagnosis						
Blood stream infection[†]	1	(4.8)	0	(0.0)	1	(3.2)
None	20	(95.2)	10	(100.0)	30	(96.8)
Creatinine Clearance (mL/min)						
≥ 90	8	(38.1)	3	(30.0)	11	(35.5)
< 90 to ≥ 60	8	(38.1)	4	(40.0)	12	(38.7)
< 60 to ≥ 30	3	(14.3)	2	(20.0)	5	(16.1)
< 30 to ≥ 15	1	(4.8)	1	(10.0)	2	(6.5)
Not applicable	1	(4.8)	0	(0.0)	1	(3.2)
Polymicrobial Infections						
Single pathogen isolated(monomicrobial)	21	(100.0)	9	(90.0)	30	(96.8)

Multiple pathogens isolated(polymicrobial)	0	(0.0)	1	(10.0)	1	(3.2)
Bacteremia[††]						
Yes	1	(4.8)	1	(10.0)	2	(6.5)
No	5	(23.8)	2	(20.0)	7	(22.6)
Unknown[§]	15	(71.4)	7	(70.0)	22	(71.0)

[†] A secondary diagnosis of blood stream infection was recorded in the event that both the primary infection site and a blood cultures were positive for the same pathogen at baseline.

[††] Subjects with baseline blood cultures showing the presence of bacteria, regardless of antimicrobial susceptibility profile.

[§] Baseline blood culture not collected.

IMI = imipenem/cilastatin; REL = relebactam; CMS = colistimethate sodium.

HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection.

UT = urinary tract.

APACHE = acute physiological and chronic health evaluation.

Overall, the mean APACHE II score was 11.5. The mean APACHE II scores were higher for subjects with HAP/VAP (15.9) and cIAI (16.3), than in subjects with cUTI (7.3).

Of the 16 subjects with cUTI in the mMITT population, 8 had acute pyelonephritis with a normal urinary tract and 8 had cUTI due to underlying urinary tract abnormalities. The diagnoses for the 4 subjects with cIAI in the mMITT population were perforated hollow viscus (n=2), peritonitis (n=1), and intra-abdominal abscess (n=2). In the mMITT population, of the 11 subjects in the HAP/VAP infection-site stratum, 2 subjects had a primary diagnosis of HAP, and 9 subjects had a primary diagnosis of VAP. The most common radiologic findings in the mMITT population were pleural effusion (comparable between the 2 treatment groups) and pulmonary consolidation (more common in Treatment Group 1).

Baseline microbiology

All qualifying pathogens were aerobic gram-negative bacilli, and most were *P. aeruginosa*. The remainder were Enterobacteriaceae; of these, *K. pneumoniae* was the most common.

Table E4. Qualifying baseline pathogens (mMITT population)

	Treatment Group 1: IMI/REL + Placebo for CMS		Treatment Group 2: CMS + IMI		Total	
	N	n (%)	N	n (%)	N	n (%)
All Pathogens	**21**	**21**	**10**	**10**	**31**	**31**
Aerobic Gram-Negative Bacillus	**21**	**21 (100.0)**	**10**	**10 (100.0)**	**31**	**31 (100.0)**
Citrobacter freundii	1	1 (4.8)	0	0 (0.0)	1	1 (3.2)
Enterobacter cloacae	1	1 (4.8)	0	0 (0.0)	1	1 (3.2)
Klebsiella oxytoca	0	0 (0.0)	1	1 (10.0)	1	1 (3.2)
Klebsiella pneumoniae	3	3 (14.3)	1	1 (10.0)	4	4 (12.9)
Pseudomonas aeruginosa	16	16 (76.2)	8	8 (80.0)	24	24 (77.4)

IMI = imipenem/cilastatin; REL = relebactam; CMS = colistimethate sodium.

N = The number of subjects who have the corresponding qualifying baseline pathogen.

n = The number of isolated pathogens within each category.

Among the 24 *P. aeruginosa* isolates, all carried the chromosomally encoded Ambler class C cephalosporinase AmpC of which there were 17 alleles detected. Eight isolates also carried class A ESBLs. Among the 8 Enterobacteriaceae, KPCs (both KPC-2 and KPC-3) were carried by 5 pathogens. Class A ESBLs were carried by seven isolates. Plasmid-borne AmpCs (2 isolates) and OXA-48 (1 isolate) were also identified. Of the two *K. pneumoniae* isolates without detection of KPCs, one carried ESBLs only (SHV-1, CTX-M-15) and the other carried SHV-1, TEM-New Variant, CTX-M-15 and OXA-48. Both had borderline MICs of IMI and IMI/REL (2 and 1 mg/L, respectively) corresponding to IMI-resistance and IMI/REL-susceptibility, respectively (CLSI susceptibility testing interpretive criteria).

Numbers analysed

Analysis population	**Treatment group 1** **N (%)**	**Treatment group 2** **N (%)**
All treated	31 (100)	16 (100)
mMITT	21 (67.7)	10 (62.5)
PP	15 (48.4)	5 (31.3)

Outcomes and estimation

The majority (≥70%) of subjects in both treatment groups in the mMITT population achieved a favourable overall response and was comparable in both treatment groups. The analysis results of the key secondary endpoints supported the primary efficacy results (table below).

Table E5. Primary and key secondary endpoints (mMITT population)

	Treatment Group 1: IMI/REL + Placebo for CMS			Treatment Group 2: CMS + IMI			Unadjusted Difference	Adjusted Difference in % vs CMS + IMI	
	n	%	(95% CI)[†]	n	%	(95% CI)[†]	%	%	(90% CI)[‡]
Subjects in population	21			10					
Primary Analysis									
Favorable overall response[§]	15	71.4	(49.8, 86.4)	7	70.0	(39.2, 89.7)	1.4	-7.3	(-27.5, 21.4)
Secondary Analyses									
Favorable clinical response at Day 28	15	71.4	(49.8, 86.4)	4	40.0	(16.7, 68.8)	31.4	26.3	(1.3, 51.5)
All-cause mortality through Day 28	2	9.5	(1.4, 30.1)	3	30.0	(10.3, 60.8)	-20.5	-17.3	(-46.4, 6.7)

IMI = imipenem/cilastatin; REL = relebactam; CMS = colistimethate sodium.

[†] 95% confidence intervals are based on Agresti & Coull method.

[‡] Adjusted differences and 90% confidence intervals are based on Miettinen & Nurminen method stratified by infection-site stratum.

[§] Overall response:(a) survival status through Day 28 post-randomization in subjects with HABP/VABP, (b) clinical response at Day 28 post-randomization for subjects with cIAI and (c) the composite clinical and microbiological response at EFU for subjects with cUTI.

Results for the PP population for the primary endpoint were comparable to those observed for the mMITT population with a favourable response in 13/15 (86.7%) and 4/5 (80.0%) for treatment groups 1 and 2, respectively.

Alternate definition of favourable overall response in the mMITT population

When the microbiological response (for cUTI) and clinical response (for cIAI and HAP/VAP) at early follow-up was evaluated which is consistent with CHMP guidance for evaluation of these conditions, a lower percentage of subjects achieved a favourable overall response in both treatment groups (66.7% in Treatment Group 1 and 50.0% in Treatment Group 2) than when using the primary endpoint definition. This was due to 3 subjects with HAP/VAP (1 in Treatment Group 1, 2 in Treatment Group 2) who had unfavourable responses using the alternate definition (clinical response at the EFU Visit) but had favourable response using the primary endpoint definition (survival at Day 28).

Table E6. Favourable overall response – Alternate definition (mMITT population)

	Treatment Group 1: IMI/REL + Placebo for CMS			Treatment Group 2: CMS + IMI			Unadjusted Difference	Adjusted Difference in % vs CMS + IMI	
	n	%	(95% CI)[†]	n	%	(95% CI)[†]	%	%	(90% CI)[‡]
Subjects in population	21			10					
Favorable overall response[§]	14	66.7	(45.2, 83.0)	5	50.0	(23.7, 76.3)	16.7	10.6	(-13.9, 39.9)

IMI = imipenem/cilastatin; REL = relebactam; CMS = colistimethate sodium.

[†] 95% confidence intervals are based on Agresti & Coull method.

[‡] Adjusted difference and 90% confidence interval are based on Miettinen & Nurminen method stratified by infection-site stratum.

[§] Overall response:(a) clinical response at the early follow-up visit (EFU), for subjects with HABP/VABP, (b) clinical response at EFU, for subjects with cIAI, and (c) the microbiological response at EFU for subjects with cUTI.

Ancillary analyses

Key secondary analyses

Favourable clinical response at day 28 was 71.4 and 40.0% for groups 1 and 2, respectively. The larger between-group difference observed for favourable clinical response at Day 28 (table E5 above) than for favourable overall response was driven mainly by 3 subjects in Treatment Group 2 of which 2 subjects with HAP/VAP who survived on Day 28 and therefore met criteria for favourable overall response did not meet criteria for favourable clinical response at Day 28 and 1 subject with cUTI who had favourable microbiological and clinical response at the EFU Visit and therefore met criteria for favourable overall response but did not meet criteria for a favourable clinical response at Day 28.

The all-cause mortality through day 28 in each treatment arm were 2 and 3 subjects for groups 1 and 2, respectively.

Subgroup analyses

Favourable overall response results in all subgroups were generally comparable to the results for the mMITT population as a whole.

Outcome by baseline pathogen

Three subjects in each treatment group with unfavourable response for the primary efficacy endpoint had *P. aeruginosa* as qualifying baseline pathogen and the additional two subjects in treatment group 1 with unfavourable response had an infection caused by *K. pneumoniae*.

Emergence of nonsusceptibility to trial treatment

According to CLSI and EUCAST susceptibility testing interpretive criteria, no subjects in either treatment group developed emergent resistance to trial treatments during IV treatment.

Efficacy of IMI/REL in Treatment Group 3

At EOT and Day 28, 2 of 3 subjects in Treatment Group 3 achieved a favourable clinical response. Both subjects were in the cIAI infection-site stratum and received Sponsor-approved extension of trial treatment for 41 and 42 days (EOT Visits Days 42 and 43, respectively). Therefore, the Day 28 clinical response assessment occurred while subjects were still on IV trial treatment. By the EFU Visit, neither of these subjects had a favourable clinical response. One subject had an indeterminate response; the other subject had clinical improvement but incomplete resolution.

The 1 subject in Treatment Group 3 who did not achieve a favourable clinical response at any time point was in the HABP/VABP infection-site stratum and died on Trial Day 8.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table E7. Summary of efficacy for trial PN013

Title: A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Estimate the Efficacy and Safety of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem/Cilastatin in Subjects with Imipenem-Resistant Bacterial Infection		
Study identifier	Protocol number: P013MK7655A; EudraCT: 2015-000066-62	
Design	This was a Phase 3, randomized, double-blind, active-controlled, parallel-group, multicenter trial of IMI/REL compared with colistin + IMI in adult subjects with IMI non-susceptible bacterial infections, including HAP/VAP, cIAI, and cUTI. Subjects with IMI non-susceptible bacterial infection (with colistin and IMI/REL susceptibility) were randomized in a 2:1 ratio to IMI/REL + placebo for CMS or CMS + IMI. Randomization was stratified by infection type. In addition to the randomized subjects, eligible subjects could also be enrolled into a third non-randomized, unblinded/open-label treatment group to receive IMI/REL.	
	Duration of main phase:	Treatment phase 5 to 21 days included the OTX (on therapy) visit (day 3). Other main phase visits included the EOT (end of treatment) visit, the EFU (early follow up; 5 to 9 days post EOT) visit and the day 28 post-randomisation visit. AEs were monitored for 14 days following EOT. Not applicable
Hypothesis	This was an estimation trial mainly comparing the efficacy and safety of two parallel treatment regimens	
Treatments groups	Treatment Group 1 IMI/REL	Treatment: IMI/REL 500 mg/250 mg q6h, Duration: 5 or 7 to 21 days, Numbers randomized: 31

	Treatment Group 2 CMS+IMI		Treatment: Colistin (loading followed by maintenance doses q12h) + IMI 500 mg q6h, Duration: 5 or 7 to 21 days, Numbers randomized: 16
	Treatment Group 3 Open label IMI/REL		Treatment: IMI/REL 500 mg/250 mg q6h, Duration: 5 or 7 to 21 days, Numbers: 3
Endpoints and definitions	Primary endpoint	Favourable overall response in the mMITT population	Survival at day 28 for HAP/VAP, favourable clinical response (cure or sustained cure) for cIAI at day 28 and favourable clinical (cure or sustained cure) and microbiological response (sustained eradication) for cUTI assessed at EFU
	Key secondary endpoints	Favourable clinical response at day 28 AND All-cause mortality	Favourable clinical response (cure or sustained cure at day 28 AND The incidence of all-cause mortality within 28 days after initiation of trial treatment
	Alternate definition of the primary endpoint	Favourable overall response in the mMITT population	Favourable clinical response at EFU for HAP/VAP and cIAI and favourable microbiological response at EFU for cUTI
Database lock	31-OCT-2017		

Results and Analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Microbiological modified Intent to treat population (all randomised subjects who received at least 1 dose of study drug and who had a baseline pathogen that met inclusion criteria)			
Descriptive statistics and estimate variability	Treatment group	IMI/REL	CMS+ IMI	Open label IMI/REL
	Number of subjects	21	10	3
	Favourable overall response (%)	15 (71.4)	7 (70.0)	NA

	Adjusted difference in % (IMI/REL vs CMS+IMI) (90% CI)	-7.3 (-27.5, 21.4)		NA
Analysis description	**Key secondary analysis 1**			
Analysis population and time point description	Microbiological modified Intent to treat population			
Descriptive statistics and estimate variability	Treatment group	IMI/REL	CMS+ IMI	Open label IMI/REL
	Number of subjects	21	10	3
	Favourable clinical response at day 28 (%)	15 (71.4)	4 (40.0)	NA)
	Adjusted difference in % (IMI/REL vs CMS+IMI) (90% CI)	26.3 (1.3, 51.5)		NA
Analysis description	**Key secondary analysis 2**			
Analysis population and time point description	Microbiological modified Intent to treat population			
Descriptive statistics and estimate variability	Treatment group	IMI/REL	CMS+ IMI	Open label IMI/REL
	Number of subjects	21	10	3
	All-cause mortality through day 28 (%)	2 (9.5)	3 (30.0)	1 (33.3)
	Adjusted difference in % (IMI/REL vs CMS+IMI) (90% CI)	-17.3 (-46.4, 6.7)		NA
Analysis description	**Alternate definition of the primary endpoint**			
Analysis population and time point description	Microbiological modified Intent to treat population			
Descriptive statistics and estimate variability	Treatment group	IMI/REL	CMS+ IMI	Open label IMI/REL
	Number of subjects	21	10	3
	Favourable overall response (%)	14 (66.7)	5 (50.0)	NA

	Adjusted difference in % (IMI/REL vs CMS+IMI) (90% CI)	10.6 (-13.9, 39.9)	NA

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable because phase 2 and 3 efficacy data were not combined.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PN003/PN004[1]	83/431	48/431	4/431
PN013[2]	10/34	3/34	0/34
Actual treatment group is displayed in this table [1] Number of subjects within the age category who received IMI + REL (250 or 125 mg). [2] Number of subjects within the age category who received IMI/REL in Treatment Group 1 or 3.			

Supportive studies

Two different dose levels of REL (125 mg and 250 mg) administered q6h were combined with IMI 500 mg q6h and compared with IMI 500 mg q6h alone for the treatment of hospitalised adult subjects with cUTI (PN003) and cIAI (PN004). The design of these studies is briefly described in the table E1 above. Since these studies were not enriched for IMI non-susceptible pathogens for which REL would restore the effect IMI, the different treatment arms actually compared IMI with itself at an already approved dose regimen. Therefore, although important for the assessment of safety and pharmacokinetics of REL, the studies were not expected to make a significant contribution for the assessment of the combined effect of IMI and REL.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of IMI/REL in the treatment of adults with bacterial infections due to aerobic Gram-negative microorganisms with limited treatment options has been evaluated in one phase 3 study (PN013) comparing IMI/REL with colistin + IMI for the treatment of cUTI, cIAI and HAP/VAP caused by pathogens with acquired resistance to IMI. This study was of limited size and was designed to comply with what is described in the Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial

infections (EMA/CHMP/351889/2013) with regards circumstances in which limited clinical data may be accepted for antibacterial agents with an ability to address an unmet clinical need.

The Applicant has provided a reasonable justification that IMI/REL may have an ability to fulfil an unmet need: Firstly, the increasing problem with CR in Gram-negative pathogens; secondly, few alternatives for the treatment of these pathogens are available; and thirdly, the ability of REL to restore the activity of IMI mainly against AmpC producing *P. aeruginosa* and KPC producing Enterobacteriaceae. The final acceptance of the limited clinical programme relies on a robust demonstration of the adequacy of the dose of IMI and REL in the FDC. In that respect the PK/PD analyses are considered pivotal and clinical data only supportive because of the limited size of the clinical programme.

The dose to be selected for phase 3 and proof-of-concept of the FDC was also evaluated in two phase 2 studies comparing IMI + two different doses of REL with IMI alone for the treatment of cUTI and cIAI (PN003 and PN004). It should be noted that there were no requirements in the phase 2 studies that the infections should be caused by IMI-resistant pathogens. Therefore, these studies were not capable to demonstrate the efficacy of REL in addition to IMI alone.

Study PN013

Study PN013 included hospitalised adult subjects with HAP/VAP, cIAI or cUTI. These infection types are the most likely to be caused by pathogens of interest for the evaluation of IMI/REL. In treatment groups 1 and 2 there had to be culture evidence from the primary site of infection of IMI-resistant + IMI/REL- and colistin-susceptible Gram-negative bacteria. In the open-label treatment arm to receive IMI/REL (treatment group 3) colistin-resistance was required. The study excluded patients with highest APACHE II scores (>30) and subjects with a creatinine clearance <15 mL/min. Although some CHMP recommendations made in the 2015 scientific advice seem to not have been taken into account in the study protocol, the inclusion and exclusion criteria were acceptable and seemed to not have been confounded by these deficiencies when the subject's disease characteristics were assessed.

The dose of IMI in the FDC (500 mg q6h) is within the range of recommended doses for the treatment of cIAI, severe pneumonia including HAP/VAP, intra-and post-partum infections, cUTI and cSSTI agreed during the referral under Article 30 of Directive 2001/83/EC in order to harmonise the national summary of product characteristics of Tienam and associated names (Procedure No. EMEA/H/A-30/1187). However, it should be noted that according the agreed product information for Tienam and associated names, it is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as *Pseudomonas aeruginosa*) and very severe infections should be treated with imipenem 1000 mg q6h.

The choice of a single comparative regimen instead of a best-available-therapy regimen chosen by each investigator has certainly advantages for the assessment. It is furthermore agreed that many investigators would not prefer to use colistin alone. To combine colistin with a carbapenem, although carbapenem-resistance is detected, is reasonable and there are data that combining with a carbapenem may provide survival benefit. The dose of colistin is acceptable and according the recommendation concluded in the Article 31 referral EMEA/H/A-31/1383 concluded in 2014. The dose adjustment of IMI in patients with impairment of renal function is in line with the product information and for colistin broadly in line with the label and thus acceptable.

Duration of treatment up to 21 days was questioned in the scientific advice given, since it would be usual to regard any patient who needs more than 10-14 days to be a failure. This is further discussed below.

The study primarily compared favourable overall response which in principal is acceptable when more than one infection type is included in a study. However, the primary endpoint for each infection type was not fully in line with CHMP expectations. The applicant has added an additional endpoint with an alternate definition of favourable overall response more in line with what is described in EMA/CHMP/351889/2013. However, the assessment of microbiological eradication ($<10^4$ CFU/mL) differed from what is recommended in the CHMP guideline ($<10^3$ CFU/mL).

The sample size was driven by feasibility and not by statistical considerations. The size of the study was discussed and agreed during the scientific advice received.

Study subjects were randomised to receive IMI/REL or comparator regimen and the randomisation was stratified according to infection types.

Study treatments were dispensed and administered in a double-blinded fashion for subjects in treatment groups 1 and 2. The methodologies for these procedures were deemed acceptable.

The microbiological modified intention to treat population defined as all randomised subjects who received at least one dose of IV study therapy and who had a baseline bacterial pathogen in line with inclusion criteria 3 was the primary population used for efficacy analysis. The per-protocol population served as the secondary population. The primary population as defined was reasonable. This was to focus the evaluation on subjects infected with pathogens within the spectrum of REL´s inhibitory capacity.

Between-group 90% CIs for the primary and key secondary endpoints were calculated using the stratified Miettinen and Nurminen method.

Fifty-four subjects were screened, and 50 subjects were enrolled (31, 16 and 3 subjects in the respective treatment group). A higher percentage of subjects in Treatment Group 1 compared with Treatment Group 2 completed trial treatment and completed the study. This was primarily due to a lower percentage of subjects in Treatment Group 1 who discontinued trial treatment due to an AE and who discontinued the trial due to death.

Among the 16 subjects who were excluded from the mMITT population, 13 subjects were excluded because the pathogens isolated from their infection-site culture did not meet protocol-specified susceptibility criteria. For the remaining 3 subjects, the qualifying culture was collected more than 1 week prior to entry. Most common additional reasons for exclusion from the PP population were concomitant antibacterial violation (5 subjects) and protocol-specified infection diagnosis criteria not met (3 subjects).

Treatment compliance was high in both treatment groups. The mean duration of exposure to study treatment was similar in treatment group 1 and 2.

Two subjects in each treatment group had treatment duration of 15 days or more. As discussed above and in the CHMP scientific advice given subjects with duration of therapy of more than 14 days should reasonably be considered failures.

Demographics and baseline subject characteristics were generally comparable for treatment groups 1 and 2, with the exception of age. The mean age in treatment group 1 was lower (54 vs. 63 in treatment group 2). The typical patient was a white, European male aged 41 to 64 years.

Approximately 50% of the subjects had cUTI of which half had pyelonephritis, one third had HAP/VAP of which all but two subjects had VAP. Only 13% had cIAI. The infections were generally monomicrobial and only two patients had bacteraemia. Most pathogens isolated were *P. aeruginosa* followed by *K. pneumoniae.* All qualifying baseline isolates in both treatment groups were non-susceptible (resistant or intermediate) to

IMI by CLSI interpretive criteria, as expected based on the trial entry criteria (using site interpretive criteria). In comparison, 23.8% of isolates in Treatment Group 1 and 40.0% of isolates in Treatment Group 2 were susceptible to IMI by EUCAST interpretive criteria. This is not unexpected because of different cut-offs for CLSI and EUCAST interpretive criteria. Notably, in treatment group 3 none of the pathogens met criteria eligibility, as all isolates tested susceptible to IMI and/or colistin at the central laboratory.

As expected, the most common resistance mechanism detected in *P. aeruginosa* was the chromosomally encoded Ambler class C cephalosporinase AmpC and KPC and class A ESBLs for Enterobacteriaceae.

The percentages of subjects excluded from the mMITT and PP populations were essentially similar between treatment groups 1 and 2. For reasons for exclusion from the respective analysis population, see above.

Efficacy data and additional analyses

Favourable overall response was similar between treatment groups 1 and 2 (71.4% and 70.0%, respectively). With the alternate definition of favourable overall response used for the primary efficacy endpoint (to meet CHMP guidance), the corresponding favourable overall response rates were 66.7 and 50.0% for treatment groups 1 and 2, respectively. The difference of the results between the definitions was due to 3 subjects with HAP/VAP (1 in Treatment Group 1, 2 in Treatment Group 2) who had unfavourable responses using the alternate definition (clinical response at the EFU Visit) but had favourable response using the primary endpoint definition (survival at Day 28). The results from a study of this limited size must be interpreted with caution. The uncertainties in the results are reflected by the large within and between group CIs.

As discussed above and in the CHMP scientific advice given, subjects with duration of therapy of more than 14 days should reasonably be considered as failures. Four subjects (two in each treatment group) were treated for more than 14 days. The two subjects treated with IMI/REL had a favourable outcome whereas the two subjects treated with colistin + IMI failed treatment. However, also when counting the two subjects treated with IMI/REL for more than 14 days as failures instead of successes do not significantly change the overall conclusions.

CHMP noted that the assessment of microbiological eradication ($<10^4$ CFU/mL in the study) differs from what is recommended in the CHMP guideline ($<10^3$ CFU/mL). Two additional subjects treated with IMI/REL had an unfavourable outcome using the EU criterion for microbiological eradication. However, CHMP agreed that this does not significantly change the overall conclusions.

Also, with regards the secondary endpoints favourable clinical response at day 28, all-cause mortality through day 28 and clinical response over time, the point-estimates for IMI/REL were essentially similar to the point-estimates for CMS + IMI.

The low number of subjects in each infection-site stratum makes any comparisons difficult. Nonetheless, the response by infection-site stratum was generally similar between the treatment groups. None of the four subjects with cIAI had a favourable clinical response at day 28.

The outcome in subgroups were generally comparable to the results for the mMITT population as a whole, although the small sample size of each subgroup and resulting variability is noted.

There were no evident differences of outcome by baseline pathogen. A similar number of subjects in both treatment arms with an unfavourable response had *P. aeruginosa* as qualifying pathogen and two additional subjects in treatment group 1 with an unfavourable response had *K. pneumoniae* as qualifying pathogen. No subject developed treatment emergent resistance. Susceptibility testing will be performed after authorisation and the development of resistance monitoring results will be reported with the PSURs.

In treatment group 3, at day 28, 2 subjects with cIAI achieved a favourable clinical response. However, these subjects were still on IV treatment at the day 28 assessment and treated for over 40 days. By the EFU Visit, neither of these subjects had a favourable clinical response. The 1 subject with HAP/VAP died on study day 8. Thus, all three subjects could be considered as failures.

PN003 and PN004

Overall, the phase 2 studies in cUTI and cIAI did not inform on REL efficacy.

2.5.3. Conclusions on the clinical efficacy

The limited sized PN013 study is considered supportive of efficacy of IMI/REL for the treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options. However, as this application relies on a limited clinical programme that does not independently demonstrate the efficacy of imipenem-cilastatin-relebactam, the clinical pharmacology programme, including non-clinical PK/PD analyses and PTA simulations using clinical PK data, is pivotal to the application and has been considered by CHMP during the assessment.

2.6. Clinical safety

IMI/REL is a fixed dose combination product containing imipenem, cilastatin and relebactam. Imipenem, approved for administration together with cilastatin, is considered to have a recognized safety profile.

The active substance relebactam (REL) is not previously approved.

The overall safety database for IMI/REL is based on 7 Phase I trials, 2 Phase II trials and 1 pivotal Phase III trial. A total of 658 subjects have received treatment with imipenem+relebactam (different doses) and 52 subjects have been exposed to relebactam only (different doses).

Most of the study population included in the Phase I trials were healthy adults, but one study included subjects with impaired renal function. In those 7 trials relebactam was dosed alone (25 mg, 50 mg, 125 mg, 250 mg, 500 mg, 1000 mg and 1150 mg) or administered as a co-infusion with IMI 500 mg + REL (50 mg, 125 mg, 250 mg, 375 mg, 500 mg and 625 mg), or as the FDC of IMI 500 mg/REL 250 mg. In the Phase II trials cUTI and cIAI subjects were treated either with imipenem 500mg+ relebactam 250mg, imipenem 500mg+ relebactam 125mg or imipenem+placebo. In the Phase III trial subjects with imipenem non-susceptible bacterial infections, specifically cUTI, cIAI, and hospital-acquired bacterial pneumonia (HAP)/ventilator-associated bacterial pneumonia (VAP) were treated either with the FDC IMI/REL (imipenem 500 mg/relebactam 250 mg) or imipenem+colistin.

The applicant has not provided any overall summary of safety data, except for the pooled data of the trials included in each phase, most of the safety data in this overview is therefore presented by each phase separately.

One additional Phase III trial (P014) in HAP/VAP subjects is still ongoing and in March 2019 514 subjects has been recruited, of which 159 of them experienced SAEs and 104 of them died.

Patient exposure

The safety of IMI/REL has been evaluated in 658 subjects that have been exposed to different doses of imipenem+relebactam. In addition to this, 52 subjects have been exposed to different doses of relebactam alone. Of the IMI/REL treated subjects, 299 subjects (Phase I: 59, Phase II: 209, Phase III: 31) were treated intravenously for ≥4 days with the intended clinical dose of 500 mg imipenem + 250 mg relebactam.

Table 7. Summary of Subjects by Treatment Regimen in the IMI/REL Clinical Program

Treatment	Number of Subjects by Trial Phase			Total Subjects
	Phase 1[a]	Phase 2[b]	Phase 3[c]	
REL	52	0	0	52
IMI + REL	179	431	0	610
IMI/REL[d]	14	0	34	48
IMI + Placebo	33	214	0	247
CMS + IMI	0	0	16	16

Abbreviations: CMS = colistimethate sodium; IMI = imipenem/cilastatin; IMI/REL = fixed-dose combination of imipenem/cilastatin/relebactam; REL = relebactam (MK-7655).
[a] Includes 7 Phase 1 trials. A subject in a Phase 1 trial may be counted in more than one row because of crossover or fixed-sequence trial designs.
[b] Trials PN003 and PN004.
[c] Trial PN013.
[d] IMI/REL treatment includes the treatment groups that received IMI/REL alone and IMI/REL + other drugs.
Note: The numbers of subjects who received each treatment are presented regardless of dose.

Most of the subjects included in all trials where white at the age of 18-65 years. It was noted that the Phase I trials male subject were predominating (76.2%) as expected whereas in the Phase II trial the distribution was more similar between male (54.3%) and female (45.7%). In the Phase II trials, the majority (86.2%) was related to Europe as geographic region.

Adverse events

Phase I trials

Common Adverse Events

Relebactam only

The most common reported AEs (≥2%) in the Phase I trials in subjects treated with REL only (any dose) were headache (9.6%), infusion site erythema (5.8%), paraesthesia (3.8%), somnolence (3.8%) and dermatitis contact (3.8%). The most common SOC was general disorders/administration site conditions (17.3%) and nervous system disorders (15.4%).

Imipenem+relebactam

In subjects treated with any dose of IMI+REL were the most common reported AEs (≥2%) infusion site erythema (17.9%), infusion site pain (14.5%), headache (8.9%), infusion site swelling (5.6%), catheter site pain (5.6%), aspartate aminotransferase (AST) increase (5.0%), nausea (4.5%), tongue discoloration

(4.5%), alanine aminotransferase (ALT) increase (3.9%), presyncope (3.9%), diarrhoea (3.4%), erythema (2.2%) and dizziness (2.2%). The most common SOC was general disorders/administration site conditions (28.5%), gastrointestinal disorders (14.5%) and nervous system disorders (14.5%).

Drug Related Adverse Events

Relebactam only

The most common drug-related AEs (≥2%) in the Phase I trials in subject treated with REL only included infusion site erythema (5.8%), headache (3.8%), paraesthesia (3.8%), and somnolence (3.8%).

Imipenem+relebactam

The most common drug-related AEs (≥2%) in the Phase I trials treated with IMI + REL were infusion site erythema (17.9%), infusion site pain (14.0%), infusion site swelling (5.6%), AST increase (4.5%), tongue discoloration (4.5%), diarrhoea (3.4%), nausea (3.4%), AST increase (3.4%) and headache (3.4%).

Phase II trials

The most common reported adverse events among subjects treated with imipenem+relebactam 250 mg in the two Phase II trials were diarrhoea (5.6%), nausea (5.6%), headache (4.2%), vomiting (3.2%), and ALT increased (3.2%).

Table 8. The Most Commonly Reported Adverse Events during Study Therapy or 14-Day Follow-Up Period (Incidence ⩾ 2% in One or More Treatment Groups) in the Phase II Trials.

	IMI + REL 250 mg		IMI + REL 125 mg		IMI + Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	216		215		214		645	
with one or more adverse events	85	(39.4)	84	(39.1)	77	(36.0)	246	(38.1)
with no adverse events	131	(60.6)	131	(60.9)	137	(64.0)	399	(61.9)
Blood and lymphatic system disorders	**7**	**(3.2)**	**4**	**(1.9)**	**6**	**(2.8)**	**17**	**(2.6)**
Thrombocytosis	5	(2.3)	1	(0.5)	2	(0.9)	8	(1.2)
Cardiac disorders	**3**	**(1.4)**	**5**	**(2.3)**	**3**	**(1.4)**	**11**	**(1.7)**
Gastrointestinal disorders	**35**	**(16.2)**	**30**	**(14.0)**	**24**	**(11.2)**	**89**	**(13.8)**
Diarrhoea	12	(5.6)	9	(4.2)	9	(4.2)	30	(4.7)
Nausea	12	(5.6)	15	(7.0)	12	(5.6)	39	(6.0)
Vomiting	7	(3.2)	10	(4.7)	4	(1.9)	21	(3.3)
General disorders and administration site conditions	**12**	**(5.6)**	**7**	**(3.3)**	**6**	**(2.8)**	**25**	**(3.9)**
Pyrexia	5	(2.3)	0	(0.0)	3	(1.4)	8	(1.2)
Infections and infestations	**21**	**(9.7)**	**15**	**(7.0)**	**15**	**(7.0)**	**51**	**(7.9)**
Postoperative wound infection	3	(1.4)	2	(0.9)	5	(2.3)	10	(1.6)
Injury, poisoning and procedural complications	**5**	**(2.3)**	**8**	**(3.7)**	**6**	**(2.8)**	**19**	**(2.9)**
Seroma	1	(0.5)	5	(2.3)	0	(0.0)	6	(0.9)
Investigations	**18**	**(8.3)**	**18**	**(8.4)**	**21**	**(9.8)**	**57**	**(8.8)**
Alanine aminotransferase increased	7	(3.2)	6	(2.8)	4	(1.9)	17	(2.6)
Aspartate aminotransferase increased	6	(2.8)	7	(3.3)	3	(1.4)	16	(2.5)
White blood cells urine positive	1	(0.5)	1	(0.5)	5	(2.3)	7	(1.1)
Nervous system disorders	**9**	**(4.2)**	**10**	**(4.7)**	**9**	**(4.2)**	**28**	**(4.3)**
Headache	9	(4.2)	5	(2.3)	5	(2.3)	19	(2.9)

Renal and urinary disorders	**4**	**(1.9)**	**2**	**(0.9)**	**6**	**(2.8)**	**12**	**(1.9)**
Respiratory, thoracic and mediastinal disorders	**4**	**(1.9)**	**6**	**(2.8)**	**9**	**(4.2)**	**19**	**(2.9)**
Skin and subcutaneous tissue disorders	**8**	**(3.7)**	**3**	**(1.4)**	**3**	**(1.4)**	**14**	**(2.2)**
Vascular disorders	**6**	**(2.8)**	**10**	**(4.7)**	**10**	**(4.7)**	**26**	**(4.0)**
Hypertension	3	(1.4)	5	(2.3)	5	(2.3)	13	(2.0)

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 = imipenem/cilastatin; REL = relebactam.

Drug related Adverse Events

The most common reported drug related AEs reported in subjects treated with imipenem + 250 mg relebactam was diarrhoea (3.7%), nausea (1.4%), increased ALT (1.4%), and increased AST (1.4%) .

Table 9. Subjects Reported with Drug-Related Adverse Events during Study Therapy and 14-Day Follow-Up Period (PN003 and PN004)

	IMI + REL 250 mg		IMI + REL 125 mg		IMI + Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	216		215		214		645	
with one or more adverse events	26	(12.0)	25	(11.6)	20	(9.3)	71	(11.0)
with no adverse events	190	(88.0)	190	(88.4)	194	(90.7)	574	(89.0)
Blood and lymphatic system disorders	**2**	**(0.9)**	**0**	**(0.0)**	**2**	**(0.9)**	**4**	**(0.6)**
Anaemia	1	(0.5)	0	(0.0)	1	(0.5)	2	(0.3)
Thrombocytopenia	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Thrombocytosis	1	(0.5)	0	(0.0)	1	(0.5)	2	(0.3)
Cardiac disorders	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.2)**
Palpitations	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(0.2)**
Vertigo	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Gastrointestinal disorders	**12**	**(5.6)**	**10**	**(4.7)**	**13**	**(6.1)**	**35**	**(5.4)**
Abdominal pain	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Abdominal pain upper	1	(0.5)	1	(0.5)	0	(0.0)	2	(0.3)
Diarrhoea	8	(3.7)	2	(0.9)	5	(2.3)	15	(2.3)
Gastritis	1	(0.5)	1	(0.5)	0	(0.0)	2	(0.3)
Ileus paralytic[†]	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Nausea	3	(1.4)	4	(1.9)	8	(3.7)	15	(2.3)
Salivary hypersecretion	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.3)
Tooth discolouration	0	(0.0)	2	(0.9)	0	(0.0)	2	(0.3)
Vomiting	1	(0.5)	0	(0.0)	3	(1.4)	4	(0.6)
General disorders and administration site conditions	**3**	**(1.4)**	**2**	**(0.9)**	**3**	**(1.4)**	**8**	**(1.2)**
Feeling of body temperature change	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Infusion site erythema	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Infusion site pain	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Infusion site phlebitis	2	(0.9)	0	(0.0)	0	(0.0)	2	(0.3)
Oedema peripheral	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)

General disorders and administration site conditions	**3**	**(1.4)**	**2**	**(0.9)**	**3**	**(1.4)**	**8**	**(1.2)**
Peripheral swelling	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Pyrexia	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Vessel puncture site rash	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Infections and infestations	**1**	**(0.5)**	**3**	**(1.4)**	**0**	**(0.0)**	**4**	**(0.6)**
Clostridium difficile colitis	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Oral candidiasis	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Vulvovaginal candidiasis	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Vulvovaginal mycotic infection	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Investigations	**5**	**(2.3)**	**6**	**(2.8)**	**5**	**(2.3)**	**16**	**(2.5)**
Alanine aminotransferase increased	3	(1.4)	3	(1.4)	3	(1.4)	9	(1.4)
Amylase increased	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Aspartate aminotransferase increased	3	(1.4)	3	(1.4)	2	(0.9)	8	(1.2)
Blood alkaline phosphatase increased	1	(0.5)	3	(1.4)	1	(0.5)	5	(0.8)
Creatinine renal clearance decreased	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Lipase increased	2	(0.9)	0	(0.0)	2	(0.9)	4	(0.6)
Platelet count increased	1	(0.5)	1	(0.5)	1	(0.5)	3	(0.5)
Metabolism and nutrition disorders	**1**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Hyperkalaemia	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Musculoskeletal and connective tissue disorders	**1**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Myalgia	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Nervous system disorders	**2**	**(0.9)**	**3**	**(1.4)**	**3**	**(1.4)**	**8**	**(1.2)**
Dizziness	1	(0.5)	0	(0.0)	1	(0.5)	2	(0.3)
Nervous system disorders	**2**	**(0.9)**	**3**	**(1.4)**	**3**	**(1.4)**	**8**	**(1.2)**
Dysgeusia	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Headache	2	(0.9)	2	(0.9)	2	(0.9)	6	(0.9)
Skin and subcutaneous tissue disorders	**3**	**(1.4)**	**0**	**(0.0)**	**1**	**(0.5)**	**4**	**(0.6)**
Pruritus generalised	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Rash	2	(0.9)	0	(0.0)	0	(0.0)	2	(0.3)
Rash generalised	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Vascular disorders	**1**	**(0.5)**	**3**	**(1.4)**	**0**	**(0.0)**	**4**	**(0.6)**
Hypotension	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Phlebitis	1	(0.5)	2	(0.9)	0	(0.0)	3	(0.5)

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.

† During final reconciliation of data associated with the serious adverse event of Ileus paralytic reported for subject 400265 (IMI + REL 250 mg group), the site responded to safety queries indicating that the event was not related to study drug. The change in causality was not implemented on the AE form within the clinical database (EDC). As a result, the correct causality is not reflected within the datasets or final CSR tables. According to the most recent SAE narrative from the primary investigator, the event of Ileus paralytic experienced by Subject 400265 (IMI + REL 250 mg group) was actually not drug-related.

IMI = imipenem/cilastatin; REL = relebactam.

The frequency of subjects who experienced one or more local infusion site reaction was slightly higher among the IMI+REL 250 mg (20.8%) compared to IMI+placebo (15.0%), of which erythema, pain, tenderness, warmth and swelling was most commonly reported. Infusion site erythema, phlebitis and infusion site pain has been proposed by the applicant to be included in section 4.8 at the frequency of common and uncommon.

The frequency of drug related increased levels of liver transaminases was similar between subjects treated with imipenem+REL and imipenem+placebo. Four subjects (2 who were treated with IMP+REL 250 mg and 2 who were treated with IMP+placebo) had elevated aspartate aminotransferase (AST) or alanine transaminase

(ALT) value ≥5 X upper limit of normal ULN which was considered by the investigator to be drug related. A warning in the Recarbrio SmPC section 4.4, in line with the outcome of the Article 30 referral for Tienam, has been included.

Phase III trial

This phase III trial included a limited number of vulnerable subjects often suffering from multiple diseases and the results should therefore be interpreted with caution. The most commonly reported AEs among the 31 IMI/REL treated subjects were pyrexia (12.9%), increased aspartate aminotransferase (AST) (9.7%) and dyspnoea (9.7%). Among the drug related adverse events was the following reported among the IMI/REL treated subjects: decreased creatinine renal clearance (6.5%) and infusion site erythema, pyrexia, & hyperglycemia (each 3.2%). Due to the limited study population it is however difficult to allow establishing of frequencies based on the observed AEs.

One of the subjects (with a history including pyelonephritis) treated with IMI/REL experienced a nephrotoxicity related adverse event which was handled by a dose adjustment of study drug in line with the SmPC recommendations.

Adverse reactions as presented in the SmPC

In the Recarbrio SmPC section 4.8, the applicant has presented a table including adverse events based on the results of the two phase II trials and based on adverse reactions previously known for imipenem/cilastatin. The phase III trial included a small number of subjects who received IMI/REL, of which a majority were suffering from comorbid conditions (N=34), and the data were therefore not included in section 4.8 in the SmPC since the frequency can be misleading. The Applicant was requested however to also include in the SmPC all AEs known for the well characterized safety profile of imipenem/cilastatin.

Serious adverse events and deaths

No serious adverse event or deaths was reported from the 7 studies included in the Phase I trials.

Deaths

Five deaths were reported in the Phase II trials (2 subjects treated with IMI+REL 250 mg and 3 subjects treated with IMI+REL 125 mg) none of them were considered related to treatment with IMI/REL which can be agreed since other diseases presented were more likely to cause the outcome of death. Among the IMI/REL treated subjects in the Phase III study three death were reported. These events occurred in subjects with several co-existing diseases and none of the deaths was considered related to study drug by the investigator, which can be agreed.

Serious Adverse Events

It can be concluded that few SAEs were reported in the Phase II (IMI+REL250 mg 3.2%) and Phase III (IMI/REL 9.7%) trials. The SOC where most IMP+REL250 mg (phase II) treated subjects were reported with SAEs was gastrointestinal disorders (1.4%) of which one subject experienced SAE of diarrhoea that was considered related to study drug.

The only drug related SAE in the Phase III trial open label was one generalised tonic-clonic seizure that was considered drug related by the investigator. No firm conclusions can be drawn based on one case reported

from a vulnerable and multi-diseased group of subjects. Seizures have been described as an uncommon adverse event related to treatment with imipenem/cilastatin.

Laboratory findings

Haematology

Overall, few abnormalities in haematology were reported.

Three events of abnormal lymphocyte morphology were reported from the Phase I trials.

During the IV treatment period of IMI+REL 250 mg and the 14 day follow up period in the Phase II trials was events of anaemia (2/216), iron deficiency anaemia (1/216), leucocytosis (1/216), and thrombocytosis (5/216) reported.

During the IV treatment period of IMI/REL and the 14 day follow up period in the Phase III trial was events of anaemia (2/31) and leucocytosis (1/31) reported.

Liver Function Tests

In the Phase I trials, increased levels of ALT (3.9%) and increased AST (5%) was reported in healthy subjects treated with IMI+REL (dose information was not included). In addition, several subjects in study PN001 and PN012 had increased levels of liver transaminases (<3X ULN) that for unknown reasons were not reported as adverse events. The elevations were not reported to be dose dependent (relebactam) and did not result in clinical signs.

No clinically relevant elevation in bilirubin was reported in any of the phase I trials and none of the subjects included met the criteria for suspected drug-induced liver injury.

Table 10. Subjects in the Phase II trials with Reported Changes in Liver Function Tests

Treatment	n	(%)	Difference in % vs IMI + Placebo	
			Estimate (95% CI)[†]	P-value[†]
Subjects in population				
IMI + REL 250 mg	216			
IMI + REL 125 mg	215			
IMI + Placebo	214			
Subjects with ECI #1				
IMI + REL 250 mg	3	(1.4)	0.5 (-2.1, 3.2)	0.661
IMI + REL 125 mg	1	(0.5)	-0.5 (-2.9, 1.7)	0.560
IMI + Placebo	2	(0.9)		
Confirmed ALT ≥ 5 X ULN				
IMI + REL 250 mg	2	(0.9)	0.9 (-0.8, 3.3)	0.159
IMI + REL 125 mg	0	(0.0)	0.0 (-1.8, 1.8)	>0.999
IMI + Placebo	0	(0.0)		
Confirmed AST ≥ 5 X ULN				
IMI + REL 250 mg	1	(0.5)	-0.5 (-2.9, 1.7)	0.557
IMI + REL 125 mg	1	(0.5)	-0.5 (-2.9, 1.7)	0.560
IMI + Placebo	2	(0.9)		
Subjects with ECI #2				
AST or ALT ≥ 3 X ULN and Total Bilirubin ≥ 2 X ULN and ALP < 2 X ULN				
IMI + REL 250 mg	1	(0.5)	0.5 (-1.3, 2.6)	0.320
IMI + REL 125 mg	0	(0.0)	0.0 (-1.8, 1.8)	>0.999
IMI + Placebo	0	(0.0)		

ECI #1: A confirmed (i.e., verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 5 X ULN as a result of within-protocol-specific testing or unscheduled testing.
ECI #2: An elevated AST or ALT laboratory value that is greater than or equal to 3 X ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 X ULN and,at the same time, an alkaline phosphatase laboratory value that is less than 2 X ULN, as a result of within-protocol-specific testing or unscheduled testing.
[†] Difference in percentage, 95% CI and P-value are based on unconditional and asymptotic Miettinen & Nurminen method without stratification.
IMI = imipenem/cilastatin; REL = relebactam.

In the Phase III trial increased ALT (2/31 [6.5%]) and increased AST (3/31 [9.7%]) was reported in few subjects.

A recommendation of closely monitoring of hepatic function during treatment was included in section 4.4, in line with the Article 30 referral for Tienam.

Renal Function

In the Phase I trials, the overall incidence of AEs within the SOC of renal and urinary disorders was low (haematuria in one subject treated with IMI+REL), as was the overall incidence of relevant AEs within the SOC of investigations (increased levels of creatinine in one subject treated with IMI+REL).

In the Phase II trials, one (1/216) of the subjects treated with IMI+REL 250 mg, one of the (1/215) subjects treated with IMI+REL 125 mg and three of the subjects (3/214) in the IMI+Placebo were reported with increased levels of creatinine in blood. Among the subjects treated with IMI+REL 125 mg decrease in creatinine based renal clearance was reported in one subject (1/215), acute kidney injury was reported in another (1/215); both adverse events led to treatment discontinuation.

In the phase III trial PN013 the percentage of patients with treatment emergent nephrotoxicity who received Recarbrio was 10.3% (3/29) and in patients who received colistin plus IMI 56.3% (9/16).

Urinalysis Parameters

Within all trials, few subjects were reported with abnormal urinalysis parameters.

Vital Signs

Few abnormalities were reported within this section. One IMI+REL treated subject in the Phase I trials and one IMI+REL treated subject in the Phase II trial experienced one event of increased blood pressure.

Safety in special populations

Data from Phase II safety population support the safety imipenem/relebactam irrespectively of age, gender and race ethnicity since the safety profiles were roughly similar.

Renal function status

Relebactam and imipenem are both primarily renally excreted. One single dose of IMP/REL appeared to be well tolerated in the limited number of subjects with renal impairment treated in study PN005, however, it is difficult to draw any firm conclusion based on one single dose administered to few subjects. In the Phase II trials, 66, 29, and 1 subjects with mild, moderate, and severe impaired renal function, respectively, were treated with imipenem+250 mg relebactam; and 75, 27, and 1 subjects with mild, moderate, and severe impaired renal function, respectively, were treated with imipenem+125 mg relebactam. Both doses seemed to be well tolerated.

Use in pregnancy and lactation

Women who were pregnant and/or lactating have been excluded from enrolment into any of the clinical trials for IMI/REL to date. No pregnancies have been reported in any of the completed clinical trials. There are no adequate and well-controlled studies of IMI/REL or its components in pregnant women.

Geriatric patients

Observed adverse events are presented by age groups are described in the tables below:

Table 11. Adverse events by age groups, phase II trials (PN003 and PN004)

Subjects in IMI+REL Group with Selected Adverse Events by Age Group (Incidence > 0% in Any Column)
During IV Therapy and 14-Day Follow-Up
MK7655A-003/004
All Subjects as Treated

MedDRA Term	Age < 65 (N=296) n (%)	Age 65 - 74 (N=83) n (%)	Age 75 - 84 (N=48) n (%)	Age 85+ (N=4) n (%)
Total AEs	119 (40.2)	30 (36.1)	18 (37.5)	2 (50.0)
Serious AEs	9 (3.0)	5 (6.0)	4 (8.3)	1 (25.0)
Fatal	0 (0.0)	2 (2.4)	1 (2.1)	0 (0.0)
Hospitalization/prolong existing hospitalization	7 (2.4)	2 (2.4)	3 (6.3)	1 (25.0)
Life-threatening	1 (0.3)	0 (0.0)	1 (2.1)	0 (0.0)
Disability/incapacity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other (medically significant)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE leading to drop-out	4 (1.4)	4 (4.8)	2 (4.2)	0 (0.0)
Psychiatric disorders	3 (1.0)	3 (3.6)	2 (4.2)	0 (0.0)
Nervous system disorders	16 (5.4)	2 (2.4)	0 (0.0)	1 (25.0)
Accidents and injuries	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	1 (0.3)	2 (2.4)	3 (6.3)	2 (50.0)
Vascular disorders	11 (3.7)	3 (3.6)	2 (4.2)	0 (0.0)
Cerebrovascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
Infections and infestations	20 (6.8)	9 (10.8)	7 (14.6)	0 (0.0)
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	0 (0.0)	0 (0.0)	0 (0.0)	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.

Table 12. Adverse events by age groups, phase III trial (PN013)

Subjects in IMI+REL Group with Selected Adverse Events by Age Group (Incidence > 0% in Any Column)
During IV Therapy and 14-Day Follow-Up
MK7655A-013
All Subjects as Treated

MedDRA Term	Age < 65 (N=21) n (%)	Age 65 - 74 (N=10) n (%)	Age 75 - 84 (N=3) n (%)	Age 85+ (N=0) n (%)
Total AEs	15 (71.4)	9 (90.0)	1 (33.3)	0
Serious AEs	4 (19.0)	1 (10.0)	1 (33.3)	0
Fatal	2 (9.5)	0 (0.0)	1 (33.3)	0
Hospitalization/prolong existing hospitalization	4 (19.0)	1 (10.0)	0 (0.0)	0
Life-threatening	3 (14.3)	0 (0.0)	0 (0.0)	0
Disability/incapacity	0 (0.0)	0 (0.0)	0 (0.0)	0
Other (medically significant)	0 (0.0)	0 (0.0)	0 (0.0)	0
AE leading to drop-out	1 (4.8)	0 (0.0)	0 (0.0)	0
Psychiatric disorders	3 (14.3)	1 (10.0)	0 (0.0)	0
Nervous system disorders	1 (4.8)	0 (0.0)	0 (0.0)	0
Accidents and injuries	1 (4.8)	0 (0.0)	0 (0.0)	0
Cardiac disorders	3 (14.3)	0 (0.0)	1 (33.3)	0
Vascular disorders	1 (4.8)	0 (0.0)	0 (0.0)	0
Cerebrovascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0
Infections and infestations	9 (42.9)	2 (20.0)	1 (33.3)	0
Anticholinergic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	0 (0.0)	0 (0.0)	0 (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.

Immunological events

Hypersensitivity reactions are known adverse events related to treatment with beta-lactams and the reactions observed in the phase II and III trials are described in the tables below. In the phase I trials, five subjects discontinued treatment due to rash-related AEs, considered drug-related by the investigator: 3 in the IMI+REL group (1 mild rash; 1 moderate rash; and 1 moderate toxic skin reaction); 1 in the IMI+PBO to REL group (moderate rash); and 1 in the placebo group (mild rash). In the phase II trials, the hypersensitivity reactions were mild, however, one subject treated with IMI/REL (250 mg) discontinued due to mild rash.

Table 13. Hypersensitivity reactions reported in the phase I trials

Hypersensitivity SMQ* Adverse Events in Phase 1 Trials (7 trials)

`		Treatment Group				
	REL	**IMI+REL[b]**	**IMI/REL**	**IMI**	**IMI+PBO**	**PBO**
Total # of subjects [a]	52	179	14	16	33	58
Adverse Event (n)						
Dermatitis contact	2	1	0	0	1	0
Eczema	1	1	0	0	0	0
Eyelid oedema	1	0	0	0	0	0
Rash	0	2	0	0	1	1
Rash maculopapular	1	0	0	0	0	0
Toxic skin eruption	0	1	0	0	0	0
Treatment day of onset (range)	1-4	3-12	n/a	n/a	9-11	13

IMI=imipenem/cilastatin; REL= relebactam; PBO = placebo
IMI+REL: Imipenem/cilastatin co-infused with relebactam
IMI/REL: Imipenem/cilastatin and relebactam in fixed dose combination
PBO: matching placebo to REL or saline placebo
*MedDRA version 19.0
[a] Due to Phase 1 study designs, individual subjects may be counted in more than one treatment category.
[b] One subject discontinued prior to initiating therapy

Table 14. Hypersensitivity reactions reported in the phase II trials

Hypersensitivity SMQ* Adverse Events in Phase 2 Trials (PN003/PN004)

	Treatment Group		
	IMI+REL[a] (250 mg)	IMI+REL[a] (125 mg)	IMI+Placebo
Total # subjects	216	215	214
Adverse Event	**n (%)**	**n (%)**	**n (%)**
Palpable purpura	1 (0.5)	0	0
Rash	3 (1.4%)	1 (0.5)	1 (0.5)
Rash generalized	0	0	1 (0.5)
Treatment day of onset (range)	4-6	2	6-12

IMI= imipenem/cilastatin (500 mg); REL = relebactam; Placebo= placebo to REL
[a] IMI (500 mg) and REL were obtained from separate vials and co administered through a single canula.
*MedDRA version 18.0

Safety related to drug-drug interactions and other interactions

See pharmacokinetic part of the assessment report.

Discontinuation due to adverse events

The overall rate of discontinuation in the imipenem/relebactam treated subjects was low (Phase I, IMI+REL different doses: (8/179); Phase II: IMI+REL 250mg 250 (4/216), IMI+REL125 mg (6/215); Phase III IMI/REL: (1/34)). Therefore, discontinuation due to AEs is not considered a major concern.

Post marketing experience

The combination of imipenem/cilastatin/relebactam is not marketed in any country. Relebactam is not marketed in any country either alone or in combination 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.

2.6.1. Discussion on clinical safety

IMI/REL is a fixed dose combination product containing imipenem, cilastatin and relebactam. The intended clinical dose is 500 mg imipenem/500 mg cilastatin/250 mg relebactam administer every 6 hours. The safety profile of imipenem together with cilastatin is well known. The active substance relebactam is not previously approved. In preclinical studies, the kidney was identified as a target organ for toxicity of relebactam. In addition, irritation of the injection site was noted. In clinical studies in healthy volunteers a total of 52 subjects were treated with relebactam at doses between 25-1150 mg alone as single or multiple doses. Commonly occurring adverse events for treatment with relebactam (alone) were headache (5/52) and infusion site erythema (3/52). No dose-dependent effects of relebactam on ALT/AST elevation were observed and no clinical signs could be related. Overall, relebactam was well tolerated in healthy adult subjects.

The overall safety database for this application includes 7 Phase I trials, 2 Phase II trials and one Phase III trial. One additional Phase III trial in hospitalized HAP/VAP subjects is still ongoing and preliminary blinded safety information for the 514 subjects has been presented by the applicant.

The safety of IMI/REL has been evaluated in 658 subjects. Of these subjects, 299 were treated intravenously for ≥4 days with the intended clinical dose of 500 mg imipenem + 250 mg relebactam. Thus, a reasonable number of patients have been exposed even though the safety data base is small.

The studied population treated with the intended clinical dose of IMI/REL consists mainly of patients with cUTI and cIAI (N=216 Phase II studies, N=23 Phase III study) whereas a small number of subjects (N= 11) with HAP/VAP were treated with IMI/REL in the Phase III study. The subjects with HAP/VAP were suffering from comorbid diseases and it is therefore not possible to draw any firm conclusions from the phase III study.

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+REL250 mg treated subjects in the Phase II trials were adverse events such as diarrhoea, duodenal ulcer perforation, pyrexia, and rash (one subject each).

Among the subjects included in the two Phase II trials treated with 500 mg imipenem+250 mg relebactam the most commonly reported adverse events were diarrhoea (5.6%; 12/216), nausea (5.6%; 12/216), vomiting (3.2%, 7/216), increased levels of AST (2.8%; 6/216), increased levels of ALT (3.2%; 7/216), headache (4.2%; 9/216), thrombocytosis (2.3%; 5/216) and pyrexia (2.3%; 5/216). In this population, the most commonly reported drug related adverse event was diarrhoea (3.7%; 8/216), nausea (1.4%; 3/216), increased ALT (1.4%; 3/216), increased AST (1.4%; 3/216).

The most commonly reported adverse events in the IMI/REL treated subjects in the Phase III study were pyrexia (12.9%; 4/31), increased AST (9.7%; 3/31) and dyspnoea (9.7%; 3/31). In this population, the most commonly reported drug related adverse event was decreased creatinine renal clearance (6.5%; 2/31).

The frequency of drug related increased levels of liver transaminases was similar between subjects treated with IMI+REL and IMI+placebo (Phase II studies). Four subjects (2 who were treated with IMI+REL 250 mg and 2 who were treated with IMI+placebo) had elevated aspartate aminotransferase (AST) or alanine transaminase (ALT) value ≥5 X upper limit of normal ULN which was considered by the investigator to be drug related. A recommendation of closely monitoring of hepatic function during treatment has been included in section 4.4 of the Recarbrio SmPC, in line with the conclusions of the Article 30 referral for Tienam.

Injections site reactions was reported to occur in 20.8% (45/216) of subjects treated with the intended clinical dose of IMI+REL in the Phase II studies, compared to 15% (32/214) of the subjects treated with IMI+placebo. Erythema (29/216), pain (27/216) and tenderness (20/216) were most commonly reported among IMI+REL treated subjects. Rash has also been observed in subjects treated with IMI/REL. The table in section 4.8 of the Recarbrio SmPC was updated to be in line with the well characterized safety information for imipenem/cilastatin.

The frequency of nephrotoxicity reported in the trials appeared to be low.

The Phase III trial included a small number of subjects of which a majority were suffering from comorbid conditions (N=34 who received IMI/REL). This study is therefore considered to have limited value to base frequency of adverse events on and is not sufficient to allow firm conclusions of possible adverse events related to treatment with relebactam.

2.6.2. Conclusions on the clinical safety

Although the safety database is relatively small, the emerging safety profile for imipenem/relebactam appears generally comparable to what is known for imipenem. No specific safety concerns for relebactam have been identified, and a safety profile that is similar to imipenem/cilastatin is expected. There are no outstanding safety concerns and the Application is approvable from the safety point of view.

2.7. Risk Management Plan

Safety concerns

No safety concerns have been identified in the RMP of Recarbrio.

Pharmacovigilance plan

There are no studies required forRecarbrio.

Risk minimisation measures

Not applicable, no safety concerns have been identified in the RMP of Recarbrio.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 16 July 2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of relebactam with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers relebactam to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group agreed to the use of minimum particulars for the 20 mL vial. The Group also proposed not to mention the excipients 3 times on the multilingual label and to delete the MAH logo.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Recarbrio (imipenem / cilastatin / relebactam) 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

Imipenem/cilastatin/relebactam is proposed by the Applicant to be indicated for the treatment of infections due to aerobic Gram-negative microorganisms in adults with limited treatment options.

Multi drug resistant (MDR) Gram-negative organisms such as carbapenem-resistant *P. aeruginosa* and Enterobacteriaceae are important pathogens in complicated urinary tract infections (cUTI) including

pyelonephritis, complicated intra-abdominal infections (cIAI) and hospital-acquired including ventilator-associated pneumonia (HAP/VAP).

3.1.2. Available therapies and unmet medical need

Beta-lactam antibacterial agents are commonly used to manage infections when they involve Gram-negative pathogens. 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.

3.1.3. Main clinical studies

The main study (PN013) was a randomised, double blind study of IMI/REL (500/250 mg q6h) versus colistin + IMI (500 mg q6h) in adult subjects with cUTI, cIAI and HAP/VAP caused by IMI-resistant gram-negative organisms. The study was intended only for a descriptive comparison of efficacy.

The supportive studies PN003 and PN004 were randomised, double blind studies of IMI/REL (REL=125 or 250 mg) versus IMI alone in adult subjects with cUTI and cIAI, respectively. In line with CHMP guidance and scientific advice there were no requirements in these studies that the infections should be caused by IMI-resistant pathogens. Therefore, these studies were expected to have limited value for the efficacy-evaluation of REL in addition to IMI alone. However, the studies were expected to provide safety and PK data from patients of the new active substance REL.

3.2. Favourable effects

In study PN013 the favourable overall response was 71.4% (15/21; 95% CI: 49.8, 86.4) in the IMI/REL group and 70.0% (7/10; 95% CI: 39.2, 89.7) in the colistin + IMI group.

With an alternate definition of favourable overall response used for the primary efficacy endpoint to meet CHMP guidance, the corresponding favourable overall response rates were 66.7% (14/21) and 50.0% (5/10) for IMI/REL and colistin + IMI treatment groups, respectively.

All-cause mortality through Day 28 was 9.5% (2/21) and 30.0% (3/10) for IMI/REL and colistin + IMI treatment groups, respectively.

The main support for the dose of REL in the FDC comes from murine thigh model studies in which it has been demonstrated that a REL *f*AUC to the IMI/REL MIC ratio of 7 was sufficient to achieve 2-$\log_{10}$ kill in combination with humanised or half-humanised doses of IMI against four strains of *P. aeruginosa*. It was

moreover demonstrated in the same model that essentially similar AUCs of REL was needed to achieve similar antibacterial effects against two strains of *K. pneumoniae* as against the *P. aeruginosa* strains tested. Based on simulations of probability of target attainment (PTA) using joint PK/PD targets of 40% *f*T>MIC target for IMI (corresponding to 2-$\log_{10}$ CFU reduction) and 7.5 *f*AUC/MIC for REL (corresponding to 2-$\log_{10}$ CFU reduction) it has been shown that the 500/250 mg q6h dose of IMI/REL is sufficient for the treatment of infections caused by pathogens up to an MIC of 2 mg/L for subjects in all renal function categories except those with creatinine clearance above 150 mL/min.

3.3. Uncertainties and limitations about favourable effects

Since the sample size in study PN013 is very limited, it does not form a basis for concluding on the efficacy of IMI/REL for the intended indication. Moreover, the phase two studies in cUTI and cIAI cannot either support the adequacy of the REL dose to protect IMI from Class A and Class C beta-lactamases, although relevant PK data were generated.

As this application relies on a limited clinical programme that does not independently demonstrate the efficacy of imipenem-cilastatin-relebactam, the clinical pharmacology programme, including non-clinical PK/PD analyses and PTA simulations using clinical PK data, is pivotal to the application. The efficacy demonstration for IMI/REL de facto rests on animal models, and particularly the murine thigh model.

While the efficacy demonstration rests on the translation of magnitudes (e.g., bacterial log kill) across experimental models, and where the clinical relevance of results (e.g., the selection of a PDT based on the ability to deliver a certain log kill) rests on the cross study comparison of effect sizes, there are no positive controls in the key experiments, whereby appropriate calibration is ascertained.

In the usual case, PDT selection is based on the mutual support of the animal models (particularly the murine thigh model), and HFIM or chemostat experiments. The Applicant has not provided any additional experimental support for the 6.5% *f*T>MIC IMI target when combined with REL as requested by the CHMP.

The Applicant has chosen a dose of IMI (500 mg q6h) in the FDC that alone would be adequate for the treatment of Enterobacteriaceae, but that is lower than what is recommended in EU SmPCs of imipenem-cilastatin or that was taken into account by the EUCAST (1g q6h) for the treatment of infections caused by *P. aeruginosa*. The Applicant claims that when IMI is combined with REL the dose of IMI in IMI/REL will adequately cover for both Enterobacteriaceae and *P. aeruginosa* up to the current EUCAST susceptibility breakpoints for IMI against these pathogens (2 and 4 mg/L, respectively). This is justified by a lower PK/PD target of IMI when combined with REL to achieve a 2 $\log_{10}$ reduction of colony counts derived from an *in vitro* hollow-fibre infection model experiment (6.5% *f*T>MIC) compared with the target accepted by the CHMP in the Article 30 referral for Tienam to support the current dose recommendation of IMI (40% *f*T>MIC). With regards to implication on the reliability of the HFIM model, see above.

The use of historical targets for the β-lactam alone have been considered acceptable in earlier applications for BL/BLI combinations. At CHMP request, the Applicant has updated the PTA simulations using IMI target values of 30% and 40%. The use of an IMI target of 40% %fT>MIC in the PTA simulations is considered acceptable by the CHMP.

In updated PTA simulations using a joint 40% target for IMI (corresponding to 2-$\log_{10}$ CFU reduction) and 7.5 *f*AUC/MIC for REL (corresponding to 2-$\log_{10}$ CFU reduction in both HFIM and murine thigh model studies) it has been shown that the 500/250 mg q6h dose of IMI/REL is satisfactory for the treatment of infections caused by pathogens up to an MIC of 2 mg/L for subjects in all renal function categories except those with

creatinine clearance above 150 mL/min. Based on surveillance data, the dose is considered adequate to treat the majority of *P. aeruginosa* and Enterobacteriaceae. In addition, a susceptibility breakpoint of 2 mg/L is recommended by the EUCAST for both Enterobacteriaceae and *P. aeruginosa*.

Taking into account what is recommended in the product information for EU authorised products containing IMI without the addition of REL and EUCAST recommended breakpoints for IMI alone, an IMI dose of 500 mg q6h (or 1 g q8h) is considered adequate with the exception of treatment of very severe infections and for the treatment of less susceptible bacterial species (such as *P. aeruginosa*). In these situations, 1000 mg IMI q6h is recommended. As an IMI/REL susceptibility breakpoint of 2 mg/L is recommended for *P. aeruginosa* rather than 4 mg/L (as recommended for IMI alone), for which 1000 mg q6h would be needed, the dose of IMI/REL is acceptable for the treatment of *P. aeruginosa* up to this lower breakpoint. However, the dose is not considered sufficient to reach the IMI target of 40% fT>MIC for subjects with ARC as shown by the PTA simulations above. Therefore, an IMI dose of 500 mg q6h in combination with REL is considered acceptable with inclusion in the Recarbrio SmPC of the message that the 500 mg q6h IMI dose may not be sufficient for patients with ARC. Moreover, similar wording as in the SmPC for products with IMI alone with regards dosing in neutropenic patients and those with very severe infections is included in the Recarbrio product information.

3.4. Unfavourable effects

The safety of IMI/REL has been evaluated in 658 subjects. Of these, 303 subjects were treated intravenously for ≥4 days with the intended clinical dose of 500 mg imipenem + 250 mg relebactam. The studied population treated with the intended clinical dose of IMI/REL consists mainly of patients with cUTI and cIAI (N=216 Phase II studies, N=23 Phase III study) whereas a small number of subjects (N= 11) with HAP/VAP were treated with IMI/REL in the Phase III study.

Commonly occurring adverse events for treatment with relebactam (alone) were headache (5/52) and infusion site erythema (3/52) which was observed in the Phase I trials.

The most frequent unfavourable effects associated with the intended clinical dose of imipenem/relebactam in the Phase II trials were diarrhoea (5.6%; 12/216), nausea (5.6%; 12/216), vomiting (3.2%; 7/216), increased levels of AST (2.8%; 6/216), increased levels of ALT (3.2%; 7/216), headache (4.2%; 9/216), thrombocytosis (2.3%; 5/216) and pyrexia (2.3%; 5/216) of which the following were most commonly reported adverse event considered drug related: diarrhoea (3.7%; 8/216), nausea (1.4%; 3/216), increased ALT (1.4%; 3/216), increased AST (1.4%; 3/216).

The most commonly reported adverse events in the IMI/REL treated subjects in the Phase III study were pyrexia (12.9%; 4/31), increased AST (9.7%; 3/31), dyspnoea (9.7%; 3/31) and decreased creatinine renal clearance (6.5%; 2/31) was the most commonly reported drug related adverse event.

Injections site reactions was reported to occur in 20.8% (45/216) of subjects treated with the intended clinical dose of IMI+REL in the Phase II studies, compared to 15% (32/214) of the subjects treated with IMI+placebo. Erythema (29/216), pain (27/216) and tenderness (20/216) were the most commonly specific reactions related to injection site reported among IMI+REL treated subjects.

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 250 mg treated subjects in the Phase II trials were adverse events such as diarrhoea, duodenal ulcer perforation, pyrexia, and rash (one subject each).

3.5. Uncertainties and limitations about unfavourable effects

The number of subjects with HAP/VAP, who tend to have extensive comorbid conditions, is very limited (N=34).

3.6. Effects Table

Effects Table for Imipenem/cilastatin/relebactam for the treatment of bacterial infections due to Gram-negative microorganisms in patients 18 years of age and older with limited treatment options.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Favourable overall response in the mMITT population	Survival at day 28 for HAP/VAP, favourable clinical response for cIAI at day 28 and favourable clinical and microbiological response for cUTI assessed at EFU	n/N (%)	IMI/REL 15/21 (71.4%)	Colistin + IMI 7/10 (70.0%)	Adjusted difference in % (IMI/REL vs CMS+IMI)% (90% CI): -7.3 (-27.5, 21.4) Too small sample size to conclude on effect of IMI/REL and to justify the doses of IMI and REL in the FDC	Study PN013
Dose justification	>90% probability of target attainment of IMI/REL against Enterobacteriaceae and *P. aeruginosa* with MIC-values up to 2 mg/L				PTA >90% is not reached for patients with augmented renal clearance	Clinical pharmacology programme
Unfavourable Effects						
Nausea	Outcome in the two phase II trials	n/N (%)	IMI+REL 250 mg 12/216 (5.6%)	IMI+placebo 12/214 (5.6%)		Study PN003 and PN004
Diarrhoea	Outcome in the two phase II trials		IMI+REL 250 mg 12/216 (5.6%)	IMI+placebo 9/214 (4.2%)		Study PN003 and PN004
Increased ALT	Outcome in the two phase II trials		IMI+REL 250 mg 7/216 (3.2%)	IMI+placebo 4/214 (1.9%)		Study PN003 and PN004

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Increased AST	Outcome in the two phase II trials		IMI+REL 250 mg 6/216 (2.8%)	IMI+placebo 3/214 (1.4%)		Study PN003 and PN004
Headache	Outcome in the two phase II trials		IMI+REL 250 mg 9/216 (4.2%)	IMI+placebo 5/214 (2.3%)		Study PN003 and PN004

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 antibacterial agents with an acceptable safety profile that are active against carbapenem-resistant Gram-negative organisms. The microbiology data indicate that REL can protect IMI from inactivation of Class A and C carbapenemases in Enterobacteriaceae and *P. aeruginosa* in the absence of other types of carbapenem resistance. Although IMI in the combination of REL cannot solve the problem of carbapenem resistance because of lack of activity against Class B and Class D carbapenemases, it could provide useful alternative for treatment of many infections due to carbapenem-resistant Gram-negative bacteria.

Although numerically similar favourable overall response rates were achieved for IMI/REL and colistin + IMI in study PN013, the sample size was too small to conclude on the effect of IMI/REL and to justify the doses of IMI and REL in the FDC. Because of the limited size of the clinical programme a sufficiently reliable PK/PD package to support the adequacy of the dose of IMI and REL in the FDC is pivotal. Although a higher dose of IMI would have been preferable in the FDC for the dose to be sufficient for the treatment of pathogens up to 4 mg/L and for subjects with augmented renal clearance the doses of IMI and REL are considered sufficiently supported for the treatment of most infections caused by pathogens up to an MIC of 2 mg/L which will include the majority of *P. aeruginosa* and Enterobacteriaceae.

Although the safety database is relatively small, CHMP agreed that the safety profile for IMI/REL appears overall acceptable and generally comparable to what is known for IMI alone.

3.7.2. Balance of benefits and risks

Noting that the clinical data is too limited to draw conclusions on the favourable effects of IMI/REL on its own, CHMP agreed that the PK/PD package is supportive that the doses of IMI and REL are adequate for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. However, the dose is not considered sufficient to reach the IMI target of 40% fT>MIC for subjects with ARC, as shown by the PTA simulations. Therefore, an IMI dose of 500 mg q6h in combination with REL is considered acceptable, but the message that the 500 mg q6h IMI dose may not be sufficient for patients with ARC is included in the Recarbrio SmPC. Moreover, the Recarbrio product information mentions that the dose

of Recarbrio may not be optimal for the treatment of infections in neutropenic patients and those with very severe infections.

Overall, the benefit/risk balance of Recarbrio is considered positive.

3.8. Conclusions

The benefit-risk balance of Recarbrio is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Recarbrio is not similar to Cayston and Tobi Podhaler within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Recarbrio is favourable in the following indication:

Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options (see sections 4.2, 4.4, and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that relebactam is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.