CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212819Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number	212819
Priority or Standard	Priority
Submit Date	November 16, 2018
Received Date	November 16, 2018
PDUFA Goal Date	July 16, 2019
Division/Office	Division of Anti-Infective Products (DAIP)/ Office of Antimicrobial Products (OAP)
Review Completion Date	July 9, 2019
Established/Proper Name	Imipenem, cilastatin and relebactam
(Proposed) Trade Name	RECARBRIO
Pharmacologic Class	Combination of imipenem, a carbapenem antibacterial drug, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a beta-lactamase inhibitor
Code name	MK-7655A
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Dosage form	Powder for Injection, 1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) in a single-dose vial
Applicant proposed Dosing Regimen	RECARBRIO 1.25 g is administered by intravenous infusion over 30 minutes every 6 hours; patients with creatinine clearance less than 90 mL/min require dosage reduction.
Applicant Proposed Indications/Population	• Complicated urinary tract infections, including pyelonephritis • Complicated intra-abdominal infections in patients 18 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indications/Populations	• Complicated urinary tract infections, including pyelonephritis • Complicated intra-abdominal infections in patients 18 years of age and older; As only limited clinical safety and efficacy data for RECARBRIO are currently available, reserve RECARBRIO for use in patients who have limited or no alternative treatment options.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	RECARBRIO 1.25 g is administered by intravenous infusion over 30 minutes every 6 hours; patients with creatinine clearance less than 90 mL/min require dosage reduction.

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APPEARS THIS WAY ON ORIGINAL

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Smith, Christopher
Nonclinical Reviewer	Wild, James S
Nonclinical Team Leader	Miller, Terry
Office of Clinical Pharmacology Reviewer(s)	Miglis, Cristina M Kitabi, Eliford N
Office of Clinical Pharmacology Team Leader(s)	Jang, Seong
Clinical Reviewer	Workneh, Meklit
Statistical Reviewer	Li, Xianbin
Statistical Team Leader	Higgins, Karen
Cross-Disciplinary Team Leader	Mishra, Shrimant
Deputy Division Director (OCP)	Reynolds, Kellie
Office Director (or designated signatory authority)	Cox, Edward

Additional Reviewers of Application

OPQ	Englund, Erika Lunn, George Shahjahan, Kabir M. Tiwari, Samata Chikhale, Elsbeth G Acevedo Santana, David A.
Microbiology	Grande, Kerian Goodwin, Avery (TL)
OPDP	Foss, David
OSI	Johnson, Aisha Lu, Min (TL)
OSE/DEPI	Pratt, Natasha Falconer, Monique (TL)
OSE/DMEPA	Myers, Deborah Townsend, Otto (TL)
OSE/DRISK	Moriyama, Brad T Everyhart, Liz (TL)
OSE/DPV	Gish, Paula Cao, Kelly (TL)

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	James Wild, PhD	OAP/DAIP	Sections: 5	**Select one:** __X_ Authored ___ Approved
	Signature:			
Nonclinical Supervisor	Terry Miller, PhD	OAP/DAIP	Sections: 5	**Select one:** ___ Authored __X_ Approved
	Signature:			
Clinical Pharmacology Reviewer	Cristina Miglis, PharmD, MSc	OCP/DCP IV	Sections 6	**Select one:** __x_ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED

Nonclinical ODE Associate Director	Timothy McGovern, PhD	OND/ODE	Section: 5	Select one: ___ Authored _X_ Approved
	Signature:			
Clinical Pharmacology Team Leader	Seong Jang, PhD	**OCP/DCP IV**	Section: 6	**Select one:** ___ Authored __X_ Approved
	Signature:			
Pharmacometrics Reviewer	Eliford Kitabi, PhD	OCP/DPM	Section: 6	**Select one:** __x_ Authored ___ Approved
	Signature:			
Pharmacometrics Team Leader	Chao Liu, PhD	OCP/DPM	Section:6	**Select one:** ___ Authored __X_ Approved
	Signature:			
Deputy Division Director (DCPIV)	Kellie Reynolds PharmD	OCP/DCPIV	Sections: 6	**Select one:** ___ Authored _X__ Approved
	Signature:			

DISCIPLINE	**REVIEWER**	**OFFICE/DIVISION**	**SECTIONS AUTHORED/ APPROVED**	**AUTHORED/ APPROVED**
Clinical Reviewer	Meklit Workneh, MD, MPH	OAP/DAIP	Sections: 1,2,3,4,7,8,9, 10,11,12,15.1,15.2	**Select one:** _X__ Authored ___ Approved
	Signature:			

Cross Disciplinary Clinical Team Leader	Shrimant Mishra, MD, MPH	OAP/DAIP	Sections: 1,2,3,4,5,6,7,8,9, 10,11,12,13,14,15	**Select one:** ___ Authored __X_ Approved
	Signature:			
Statistical Reviewer	Xianbin Li, PhD	OTS/OB/DBIV	Sections:7	**Select one:** __X_ Authored ___ Approved
	Signature:			
Statistical Team Leader	Karen Higgins, ScD	OTS/OB/DBIV	Sections:7	**Select one:** __X_ Authored __X_ Approved
	Signature:			
Division Deputy Director (DBIV)	Daphne Lin, PhD	OTS/OB/DBIV	Sections: 7	**Select one:** ___ Authored _X_ Approved
	Signature:			

DISCIPLINE	**REVIEWER**	**OFFICE/DIVISION**	**SECTIONS AUTHORED/ APPROVED**	**AUTHORED/ APPROVED**
Chief Project Management Staff	Carmen DeBellas, PharmD	**OAP/DAIP**	Section: 3	**Select one:** ___ Authored ___ Approved
	Signature:			

Division Director	Sumathi Nambiar, MD, MPH	OAP/DAIP	Section:1	**Select one:** ___ Authored __X_ Approved
	Signature:			
Office Director	Edward Cox, MD, MPH	OAP	Section 1	**Select one:** ___ Authored __X_ Approved
	Signature; See Signature in DARRTS			

DISCIPLINE	**REVIEWER**	**OFFICE/DIVISION**	**SECTIONS AUTHORED/ APPROVED**	**AUTHORED/ APPROVED**
Clinical Microbiology Reviewer	Kerian Grande Roche, PhD	OAP/DAIP	Section: 4.3, 15.6	Select one: __X_ Authored ___ Approved
	Signature:			
Clinical Microbiology Team Leader	Avery Goodwin, PhD	OAP/DAIP	Section: 4.3, 15.6	**Select one:** ___ Authored __X_ Approved
	Signature:			
Product Quality Team Leader	Erika Englund, PhD	OPQ/DNPI	Section: 4.2	**Select one:** ___ Authored __X_ Approved
	Signature:			
Associate Director for Labeling (DAIP)	Abimbola Adebowale, PhD	OAP/DAIP	Section:10	**Select one:** ___ Authored ___X Approved
	Signature:			

Regulatory Project Manager	Christopher Smith, PharmD, MPH, BCPS	OAP/DAIP	Sections: 3	**Select one:** ___ Authored __X_ Approved
	Signature:			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OTS/OB/DBIV	Office of Translational Sciences/Office of Biostatistics/Division of Biometrics IV

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

[Do not insert text here].

1.1 Product Introduction

Imipenem/cilastatin/relebactam (IMI/REL) for injection for intravenous use is a fixed dose combination (FDC) of imipenem/cilastatin with relebactam. Imipenem/cilastatin (IMI) is a combination of imipenem, a carbapenem antibacterial drug, and cilastatin, a renal dehydropeptidase inhibitor that limits the renal metabolism of imipenem. Imipenem was approved in the US in 1985 and is approved for several indications including urinary tract infections and intra-abdominal infections.

Relebactam is a new non-β-lactam β-lactamase inhibitor. Relebactam alone does not have antibacterial activity; it prevents degradation of IMI by some Class A and some Class C β-lactamases. Relebactam has no activity against the Class B metallo-β-lactamases or Class D β-lactamases. There is no pharmacokinetic interaction between imipenem and relebactam. The proposed indications for IMI/REL are complicated urinary tract infections (cUTI) including pyelonephritis, and complicated intrabdominal infections (cIAI) caused by susceptible gram-negative bacteria in patients with limited or no alternative treatment options. The recommended dose is 1.25 grams of RECARBRIO (500mg imipenem, 500mg cilastatin, and 250mg REL) administered every 6 hours by intravenous infusion over 30 minutes in patients 18 years or older and with a creatinine clearance (CLCr) 90 mL/min or higher; dosing adjustment is needed for renal impairment.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided adequate information to support the effectiveness of IMI/REL for the treatment of cIAI and cUTI in patients with limited or no treatment options. The substantial evidence of effectiveness of IMI/REL relies in part on the FDA's previous findings of efficacy for IMI in the treatment of cUTI and cIAI, limited clinical data from studies PN003 (cUTI), PN004 (cIAI), and PN013, and data from *in vitro* studies and from animal models of infection demonstrating that relebactam restores the activity of imipenem against imipenem-nonsusceptible gram-negative organisms expressing some Class A and some Class C β-lactamases.

IMI/REL is a combination product and the contribution of the components was required to be assessed per 21 CFR 300.50. As the components of the combination cannot be studied as monotherapy in the clinical condition of interest, contribution of the components was assessed *in vitro* and in animal models of infection as outlined in the guidance on co-development of two or more investigational drugs for use in combination. The evaluation of the contribution of relebactam to the combination relies on findings from *in vitro* microbiology and animal models of infection.

IMI/REL was studied in two trials, one in cUTI (trial PN003) and another in cIAI (trial PN004), where it was compared with imipenem alone. These trials did not specify enrollment of patients with infection due to imipenem nonsusceptible organisms only, thus the contribution of relebactam could not be evaluated in these trials. IMI/REL was also studied in a trial that enrolled patients with any of the following infections: hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia (HABP/VABP), cIAI, and cUTI caused by imipenem-nonsusceptible gram-negative bacteria (trial PN013).

Efficacy conclusions from the cIAI and cUTI trials were limited because IMI/REL was compared with IMI alone in treating infections caused by imipenem-susceptible pathogens; the contribution of REL to the combination could not be evaluated. Additionally, the analysis population considered (i.e., microbiologically-evaluable rather than microbiological intention-to-treat population), timing of the endpoints, the definition of the endpoints for the cUTI study (see Section 7.3), and choice of noninferiority (NI) margin limit the ability to draw scientifically reliable conclusions from these trials. Hence, given these multiple scientific limitations, these studies are not considered adequate and well-controlled. A posthoc assessment of these trials shows that in the cIAI trial, IMI/REL was within a margin of 12.5% (a margin currently considered acceptable to support a limited use cIAI indication). However, the clinical utility of such an assessment is limited and primarily serves to demonstrate that the addition of REL does not reduce the efficacy of IMI by a margin greater than what would have been considered acceptable for another comparator. In the cUTI trial, IMI/REL was not shown to be noninferior to IMI even using a NI margin of 15% (the margin currently considered acceptable to support a limited use cUTI indication). The trial was however not powered to demonstrate NI in the appropriate patient population and hence it is difficult to draw any definitive conclusions from this finding.

Results from trial PN013 in patients with infections due to IMI nonsusceptible organisms are difficult to interpret. This was a very small trial that was designed as a descriptive trial with no pre-specified plans for hypothesis testing. The point estimates for the clinical response rates in the IMI/REL and the comparator arm (colistin) were similar, and the point estimates for the overall mortality rates were lower in the IMI/REL arm compared to the colistin arm. However, these results are difficult to interpret, given the small sample size and hence the wide variability in results. The lack of a pre-specified analysis plan increases the likelihood of a finding of a difference in one of a number of analyses by chance. Also, assessing outcomes across different body sites in a single trial is challenging as the endpoints and outcomes are different between the various infection types studied (HABP/VABP, cUTI, cIAI). Differences in the efficacy of a drug at different body sites has been seen in clinical trials with several antibacterial drugs.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 212819, the Applicant is seeking approval of IMI/REL (RECARBRIO) for the treatment of cUTI including pyelonephritis, and cIAI in patients 18 years or older with limited or no treatment options.

IMI/REL is a fixed dose combination of IMI with relebactam. IMI was approved in the US in 1985 and is approved for several indications including urinary tract infections and intra-abdominal infections. Relebactam is a non-β-lactam β-lactamase inhibitor that prevents degradation of imipenem by some Class A and some Class C β-lactamases. Relebactam has no intrinsic antibacterial activity and there is no pharmacokinetic interaction between IMI and relebactam.

Efficacy evaluation for IMI/REL relies in part on the FDA's previous findings of efficacy of imipenem in the treatment of cUTI and cIAI. The contribution of relebactam to the combination is supported by *in vitro* and nonclinical studies demonstrating that relebactam restores activity of imipenem against imipenem-nonsusceptible gram-negative organisms expressing some Class A and some Class C β-lactamases. Limited clinical data were provided from studies PN003 (cUTI), PN004 (cIAI), and PN013. The cUTI and cIAI trials primarily enrolled patients with infections due to imipenem-susceptible organisms, so the contribution of relebactam could not be evaluated in these trials. Both trials were not designed for NI assessment using the appropriate patient populations or endpoints and were assessed descriptively. These trials primarily demonstrate that the addition of REL does not reduce the efficacy of IMI. Results of trial PN013 are difficult to interpret as it was a very small descriptive trial with no pre-specified plans for hypothesis testing. While the point estimates for the clinical response rates in the IMI/REL and the comparator arm (colistin) were similar, and the point estimates for the overall mortality rates were lower in the IMI/REL arm compared to the colistin arm, these results are difficult to interpret, given the small sample size and hence the large uncertainty. Also, assessing outcomes across different body sites in a single trial is challenging as the endpoints and outcomes are different between the various infection types studied (HABP/VABP, cUTI, cIAI) and it is difficult to achieve comparable patient populations with small numbers of patients.

No new specific safety concerns related to relebactam or to IMI/REL as compared with IMI alone were identified in nonclinical studies or in the clinical trials. In the IMI/REL clinical program, 673 subjects were exposed to any dose of IMI/REL and 304 subjects received the proposed dose of IMI/REL. While the safety database is limited, it is considered adequate for the proposed limited use indications, particularly given the known safety profile of IMI and the lack of any specific safety signals identified with relebactam alone in Phase 1 studies or in nonclinical studies.

In conclusion, the Applicant has provided substantial evidence of effectiveness of IMI/REL and the benefit-risk profile of IMI/REL is acceptable

for the treatment of cUTI including pyelonephritis, and cIAI in adults with limited or no treatment options. The safety findings observed in the trials in subjects who received the proposed dose and duration of RECARBRIO will be described in the labeling. Postmarketing requirements include pediatric studies under the Pediatric Research and Equity Act (PREA) and a microbiology surveillance study to monitor for development of resistance to IMI/REL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Complicated urinary tract infections (cUTI) are defined as UTIs with additional compromising factors such as abnormalities of the urinary tract or host defense systems. Pyelonephritis is considered a subset of cUTI regardless of the presence of underlying abnormalities of the urinary tract. The majority of cUTI is caused by Gram-negative pathogens of the family Enterobacteriaceae. • Complicated intra-abdominal infections (cIAI), defined as infections spreading beyond the hollow viscus of origin into the peritoneal space and associated with peritonitis or abscess formation are also commonly caused by Gram-negative pathogens of the family Enterobacteriaceae and anaerobic pathogens. • Resistant gram-negative cUTI and cIAI infections, in particular those with carbapenem-resistant Enterobacteriaceae (CRE) are of increasing concern because carbapenems are often last resort antibacterial drugs for infections caused by multidrug resistant organisms. CDC and WHO have released lists of critical priority pathogens for research and development of new antibacterial drugs including carbapenem-resistant *Enterobacteriaceae* (CRE).	Complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) are both serious, potentially life-threatening infections causing significant morbidity and mortality in the United States and worldwide. Increasing antimicrobial resistance among gram-negative organisms is a public health concern and cUTI and cIAI caused by CRE are of special concern due to limited treatment options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Antibacterial drugs approved for treatment of cUTI include extended-spectrum penicillins, cephalosporins, β-lactam/β-lactamase inhibitor combinations, fluoroquinolones, carbapenems, monobactams, aminoglycosides, tetracyclines and sulfonamides. • Antibacterial drugs approved for treatment of cIAI include extended-spectrum penicillins, cephalosporins, β-lactam/β-lactamase inhibitor combinations, fluoroquinolones, carbapenems, monobactams, aminoglycosides, tetracyclines, glycylcyclines, clindamycin and metronidazole. • There are some recently approved antibacterial drugs that may provide options for treatment of infections caused by resistant Gram-negative pathogens including plazomicin (2018), meropenem-vaborbactam (2017), ceftazidime-avibactam (2015), and ceftolozane-tazobactam (2014) for the treatment of cUTI and eravacycline (2018), ceftazidime-avibactam (2015), and ceftolozane-tazobactam (2014) for the treatment of cIAI. • There remains, however, the need for additional options for treatment of infections, including cIAI and cUTI, caused by CRE.	There are several classes of antibacterial drugs approved for the treatment of cUTI and cIAI. Some recently approved antibacterial drugs may provide options for treatment of infections caused by resistant Gram-negative pathogens. There remains, however, a need for additional options for the treatment of infections, including cIAI and cUTI, caused by CRE.
Benefit	• Efficacy evaluation for IMI/REL relies in part on the FDA's previous findings of efficacy of IMI in the treatment of cUTI and cIAI and the limited efficacy data from the cIAI and cUTI trials. In both these trials, IMI/REL was compared with IMI alone (regardless of imipenem susceptibility) so the contribution of REL could not be evaluated. • The contribution of relebactam to the combination is demonstrated by *in vitro* and nonclinical studies demonstrating that relebactam restores activity of imipenem against imipenem-nonsusceptible gram-negative organisms expressing some Class A and some Class C β-	The efficacy of imipenem/relebactam in the treatment of cUTI and cIAI is supported in part by the Agency's prior findings of efficacy of imipenem in the treatment of these infections. The contribution of relebactam to the combination is demonstrated by *in vitro* and nonclinical studies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	lactamases.	
Risk and Risk Management	• No new specific safety concerns were seen with relebactam alone or IMI/REL. No serious risks related to IMI/REL that would necessitate specific risk management strategies have been identified.	Labeling and routine pharmacovigilance will be adequate to communicate and monitor safety concerns with IMI/REL at this time.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐x	Clinician reported outcome (ClinRO)	Section 7.3 discusses relevant endpoints including clinician ascertained clinical response
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1 Analysis of Condition

Rising antimicrobial resistance, particularly among gram-negative organisms, is a worldwide threat to public health. Complicated urinary tract infections are defined as UTIs with additional compromising factors such as abnormalities of the urinary tract or host defense systems and are most frequently caused by Gram-negative pathogens.[1] Prevalence of cUTI in the United States is estimated at approximately 24.2 per 1000 hospital discharges, accounts for 10.5 million office visits, 2-3 million emergency room visits annually and up to 38% of all healthcare associated infections.[1-2] Complicated intra-abdominal infections (cIAI) are defined as infections spreading beyond the hollow viscus of origin and into the peritoneal space and are associated with peritonitis or abscess formation.[3] These infections are common, comprising the second most common cause of infection in intensive care units and appendicitis alone affects ~300,000 patients per year and accounts for 11 million hospital days.[3-5] Enteric pathogens are common causes of cIAI and include gram-negative and anaerobic pathogens,.

Multidrug resistance in cUTI and cIAI infections, particularly carbapenem resistance, has captured global concern. Carbapenems are often the last resort antibacterial drugs for serious infections caused by multidrug resistant (MDR) gram-negative organisms. The increasing resistance to these last resort antibacterial drugs has prompted the World Health Organization (WHO) to publish a list of priority pathogens for research and development of new antibacterials.[6] Critical priority pathogens cited include carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Enterobacteriaceae*. Rates of carbapenem resistance among these priority pathogens are rising with National Healthcare Safety Network (NHSN) data from 2014 showing that 49.5% of *A. baumannii*, 19.2% of *P. aeruginosa*, 7.9% of *K. pneumoniae* and 0.6% of *E. coli* isolates submitted to the network were carbapenem resistant.[7-8]

Carbapenem resistance can occur via carbapenemase producing (CP) or non-carbapenemase producing (non-CP) mechanisms. Non-CP carbapenem-resistant organisms (CRO) use other mechanisms of resistance including porin mutations, efflux pumps or a combination of these along with the production of ESBLs and AmpC β-lactamases. CP-producing CRO are of concern as they are the primary drivers of carbapenem resistance among gram-negative organisms globally and often associated with a high mortality.[9-10] Carbapenemases are a specific type of β-lactamase capable of cleaving the amide bond of most β-lactam rings, including those of carbapenems. The Ambler classification system classifies β-lactamases into four groups. Carbapenemases are grouped into three classes of β-lactamases: Ambler classes A, B and D. Ambler Class A includes *Klebsiella pneumoniae* carbapenemase (KPC), Ambler Class B includes the metallo- β-lactamases (MBLs) (New-Delhi metallo-beta-lactamase (NDM), Verona integron-

borne metallo-beta-lactamase (VIM) and imipenemase (IMP) types), while Ambler Class D includes the OXA enzymes.[11-12] The most common mechanism of carbapenem resistance in *Pseudomonas aeruginosa* are oprD porin mutations, rather than carbapenemases, though carbapenemases especially MBLs can also play a role in carbapenem resistance in this organism.[13] There is also evidence that Pseudomonas-derived cephalosporinases (PDCs), the major inducible AmpC cephalosporinases in *P. aeruginosa*, exhibit a low-level hydrolysis of carbapenems such as imipenem when combined with loss of permeability.[13]

These organisms are capable of causing a number of infections, including the types of infections represented in the studies submitted in support of NDA 212819. Antibacterial drugs with gram-negative activity that were recently approved by the FDA include omadacycline (2018), plazomicin (2018), eravacycline (2018), meropenem-vaborbactam (2017), ceftazidime-avibactam (2015) and ceftolozane-tazobactam (2014). Of these recent approvals, four (plazomicin, meropenem-vaborbactam, ceftazidime-avibactam, and ceftolozane-tazobactam) are approved for treatment of cUTI and three (eravacycline, ceftazidime-avibactam, and ceftolozane-tazobactam) are approved for treatment of cIAI. These treatment options are discussed in further detail in Section 2.2.

2.2 Analysis of Current Treatment Options

cIAI

Current classes of antibiotics that are available as treatment options for the proposed indications of cIAI for IMI/REL include extended-spectrum penicillins, cephalosporins, B-lactam/β-lactamase inhibitor combinations, fluoroquinolones, carbapenems, monobactams, aminoglycosides, glycylcyclines, and tetracyclines. Additionally, clindamycin and metronidazole are also specific antibiotics that are used, especially for coverage of anaerobic organisms. Table 1 lists some of the currently available treatment options for cIAI by antibacterial class. Treatment options continue to be limited by emerging resistance especially among gram-negative organisms frequently involved in intra-abdominal infections. Many of the treatment options listed are now recommended for use as part of a combination regimen including metronidazole, ciprofloxacin, aztreonam and most of the cephalosporins. Recently approved antibacterial drugs for treatment of cIAI include eravacycline (2018), ceftazidime-avibactam (2015) and ceftolozane-tazobactam (2014).

Table 1. Examples of Currently Available Treatment Options for cIAI by Antibacterial Class

Generic name	**Trade name**
Cephalosporins	
Cefepime	Maxipime

B-lactam/β-lactamase Inhibitor Combinations	
Ceftolozane-tazobactam	Zerbaxa
Ceftazidime-avibactam	Avycaz
Fluoroquinolones	
Ciprofloxacin	Cipro
Moxifloxacin	Avelox
Carbapenems	
Imipenem-cilastatin	Primaxin
Meropenem	Merrem
Ertapenem	Invanz

**Not a comprehensive list of available treatment options*

cUTI

Current classes of antibiotics that are available as treatment options for the proposed indications of cIAI for IMI/REL include extended-spectrum penicillins, cephalosporins, B-lactam/β-lactamase inhibitor combinations, fluoroquinolones, carbapenems, monobactams, aminoglycosides, polymyxins, and sulfa drugs. Table 2 lists some of the currently available treatment options for cUTI by antibacterial class. Recently approved antibacterial drugs for treatment of cUTI include plazomicin (2018), meropenem-vaborbactam (2017), ceftazidime-avibactam (2015) and ceftolozane-tazobactam (2014). Multidrug resistant gram-negative bacteria are implicated in cUTI and treatment options for these infections remains a global concern. Plazomicin is a novel aminoglycoside with activity against pathogens producing extended-spectrum beta-lactamases (ESBLs), Amp C cephalosporinases, and carbapenemases including MBLs, but not against strains of pathogens producing aminoglycoside-resistance methylase genes such as *armA* and *rmtC.*[14-15] Meropenem-vaborbactam, ceftazidime-avibactam, and ceftolozane-tazobactam are all β-lactam/β-lactamase inhibitor (BL/BLI) combinations that are further discussed in Table 3 below.

Table 2. Currently Available Treatment Options for cUTI by Antibacterial Class

Generic name	**Trade name**
Cephalosporins (parenteral 2nd, 3rd, and 4th generation)	

Ceftriaxone	Rocephin
Cefepime	Maxipime
Fluoroquinolones	
Levofloxacin	Levaquin
Carbapenems	
Imipenem-cilastatin	Primaxin
Ertapenem	Invanz
Monobactams	
Aztreonam	Azactam
Aminoglycosides	
Plazomicin	Zemdri
Sulfa	
Trimethoprim-Sulfamethoxazole	Bactrim

**Not a comprehensive list of available treatment options*

Table 3 lists examples of recently approved β-lactam/β-lactamase inhibitor combinations for treatment of cUTI, cIAI, or both.

Table 3. Examples of Recently Approved β-lactam/β-lactamase Inhibitor Combinations

Generic name	Trade name	Approval Year	Relevant Indications
Ceftolozane-tazobactam	Zerbaxa	2014	cIAI and cUTI
Ceftazidime-avibactam	Avycaz	2015	cIAI and cUTI
Meropenem-vaborbactam	Vabomere	2017	cUTI

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

IMI/REL is not marketed in the United States.

3.2 Summary of Presubmission/Submission Regulatory Activity

The investigational new drug application (IND) was submitted on September 13, 2010. Since then, the FDA has had several pre-submission discussions with the Applicant, which are summarized below. Fast Track and Qualified Infectious Disease Products (QIDP) designation for relebactam (MK-7655) was granted on September 13, 2013.

Table 4. Presubmission/Submission Regulatory History

Date	Interaction/Key Discussion Points
13 September 2010	IND 108754 filed for MK-7655 for the treatment of bacterial infections
15 September 2011	End of Phase 1 (Type B) Meeting/Agreement on completed and ongoing Phase 1 studies to support planned Phase 2 studies with close follow up for safety signals including hepatic and renal toxicity.
13 September 2013	Fast Track and Qualified Infectious Disease Products (QIDP) Designation for MK-7655 granted
5 December 2013	Type C Meeting/Clinical development meeting to gain feedback on acceptability of proposed clinical development program.
9 April 2014	FDA written responses to proposed Phase 3 trial
27 June 2014	FDA written responses to 30 May 2014 correspondence from the Applicant regarding two different proposed approaches for Phase 3 clinical development
20 April 2015	End of Phase 2 (EOP2) – Type B Meeting
17 June 2015	Initial Pediatric Study Plan (iPSP) submitted
20 August 2015	EOP2 CMC Meeting
15 May 2017	Type C Meeting/Clinical meeting to discuss PN013 cIAI cohort, proposed safety database (b) (4)
21 May 2018	FDA Conditional Acceptance of Proprietary Name
3 April 2018	Pre-NDA Meeting Clinical/Nonclinical
11 June 2018	Pre-NDA Meeting – CMC
16 November 2018	NDA is submitted

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

[Do not insert text here]

4.1 Office of Scientific Investigations (OSI)

Seven sites were selected for clinical inspection as part of PDUFA pre-approval clinical investigation and data validation. The clinical sites for inspection were chosen using the Clinical Investigator Site Selection Tool. Two sites were chosen for Protocol 003 and Protocol 013. Three sites were chosen for Protocol 004 including one in site in the United States. At the time of review completion, the final regulatory compliance classification for five of the seven sites is no action indicated (NAI). The preliminary regulatory compliance classification for one site is voluntary action indicated (VAI). The preliminary regulatory classification for one site is NAI.

The site that received the VAI compliance classification was based on randomization of subjects who met one or more of the exclusion criteria. One instance was reported as a protocol deviation and the other instance was not. There were also concomitant medications and adverse events omitted from eCRFs (two subjects for each omission).

Overall, the inspections revealed adequate adherence to the regulations and the investigational plan apart from the details noted. There were no Form FDA 483 (Inspectional Observations) issued. The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the proposed indications.

4.2 Product Quality

This NDA provides for a single strength of a fixed dose combination of cilastatin, imipenem, and relebactam (500/500/250 mg) as a sterile powder for injection presented in a single-dose vial. The only excipient in this product is sodium bicarbonate, which functions as a buffer. NDA 212819 references NDA 50587 (Primaxin) for the supporting CMC information of both cilastatin and imipenem. The supporting CMC information for the NME relebactam was submitted to the NDA. The manufacturing process for the drug product employs (b) (4)

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. All information requests and review issues have been addressed and there are no pending approvability issues. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on April 15, 2019. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

Novel Excipients: No novel excipients are used for the drug substances or the drug product. The only excipient is sodium bicarbonate (b) (4)

Comments on Impurities/Degradants of Concern

Drug Substance Impurities: The specifications for the drug substance impurities in relebactam are all below the levels qualified in nonclinical toxicology studies. The specifications for the imipenem/cilastatin drug substance impurities are considered qualified by more than 30 years of clinical use of PRIMAXIN®.

Drug Product Degradants: The specification for the (b) (4) relebactam drug product degradant, (b) (4) is below the level qualified in a nonclinical toxicology study conducted for the current NDA application. The specifications for the imipenem/cilastatin drug product degradants are considered qualified by more than 30 years of clinical use of PRIMAXIN®. Also, the specifications (b) (4) of the imipenem/cilastatin drug product degradants are below the levels qualified in a nonclinical toxicology study conducted for the current NDA application.

Residual Solvents: (b) (4) residual solvents are controlled in the drug substance specification, (b) (4) The acceptance criteria for (b) (4) solvents are at the limits specified in the ICH Q3C (R6) Guidance.

Elemental Impurities: Analysis of four batches manufactured (b) (4) were less than 30% of the permitted daily exposure identified in the ICH Q3D Guidance. (b) (4) Based on the consistent process experience, and the quality risk assessment, additional testing for elemental impurities is not considered necessary for release of commercial drug substance.

Potential Mutagenic Impurities for Relebactam: Evaluation and control of potential mutagenic impurities was conducted according to the guidelines in ICH M7. Impurities identified (b) (4) were evaluated for potential formation of mutagenic impurities. (b) (4) The assessment included *in-silico* analyses conducted for structural alerts followed by Ames testing and/or fate and purge risk assessment where appropriate. (Q)SAR assessment was performed using two complementary *in silico* models, expert rule-based model and statistical model (DEREK Nexus, Sarah Nexus, and/or CaseUltra). (b) (4)

(b) (4)

4.3 Clinical Microbiology

Since relebactam by itself does not exhibit antibacterial activity, the review evaluated the contribution of relebactam to IMI/REL. Evidence to support the contribution of REL was primarily from in vitro surveillance studies of pathogens related to the proposed indications of cUTI and cIAI, in vivo animal models of infection, and from the limited clinical trial information.

Although the clinical data were limited for this application, there does appear to be a contribution of relebactam to antibacterial activity of IMI/REL, especially against Enterobacteriaceae that express the serine carbapenemases KPC-2 and -3. From a clinical microbiology perspective, approval of this product is recommended, based on the evidence stated above and discussed below. Additional support is provided through assessments by the clinical pharmacology team as well as information on the antibacterial activity of IMI against the relevant pathogens. The full clinical microbiology review is provided in Appendix 18.6. A summary of the evidence of the contribution of relebactam to the antibacterial activity of imipenem-relebactam is below:

Summary of Evidence of the Contribution of Relebactam to the Antibacterial Activity of Imipenem-relebactam:

Activity in Vitro

Imipenem and IMI/REL were tested for in vitro antibacterial activity against a subset of gram-negative organisms associated with the cUTI and cIAI indications.

For 1729 US isolates of *P. aeruginosa*, the MIC90 was reduced from 16 mcg/mL to 2 mcg/mL in the presence of REL. REL did not affect the activity of imipenem against anaerobes for the majority of anaerobes tested and therefore anaerobes are not discussed in this summary.

The imipenem MIC90 for 5235 US isolates of Enterobacteriaceae was ≤0.5 mcg/mL and the MIC90 for IMI/REL was 0.25 mcg/mL. The MIC90 for ESBL Enterobacteriaceae for imipenem was ≤0.5 mcg/mL and was 0.25 mcg/mL with the addition of REL. The evidence for the contribution of REL was apparent among Enterobacteriaceae isolates that produced *Klebsiella pneumoniae* Carbapenemases (KPCs). The imipenem MIC90 for KPC-producing Enterobacteriaceae was ≥32 mcg/mL and was reduced to 1 mcg/mL with the addition of REL. For AmpC beta-lactamase, the MIC for imipenem was 4 mcg/mL and reduced to 0.25 mcg/mL with the addition of relebactam.

Evidence for the contribution of REL to in vitro activity of IMI/REL was also shown for some bacterial isolates in a hollow fiber infection model. The data indicated that REL administered at

250mg in combination with 500 mg imipenem, restored the antibacterial activity of imipenem among isolates that were not susceptible to imipenem (intermediate or resistant isolates). Results showed a greater than 4-log10 colony forming unit (CFU) reduction with no regrowth for up to 70 hours for the strain of *P. aeruginosa,* CLB 24227 (that had an imipenem MIC of 16 mcg/mL and an MIC in the presence of 4 mcg/mL of relebactam of 2 mcg/mL). A log10 CFU reduction was also demonstrated for Enterobacteriaceae strains such as *K. pneumoniae* CL6569, *E. coli* IHMA 516426, and *K. oxytoca* IHMA 1211369, which had greater than 5-fold reductions in MICs.

Activity in Vivo

Several animal models of infection in neutropenic mice were utilized for determining the in vivo activity of REL co-administered with IMI.

The in vivo data demonstrated the ability of relebactam to restore the antibacterial activity of imipenem against some *P. aeruginosa* and Enterobacteriaceae clinical isolates that were not susceptible to imipenem. Some of these isolates expressed beta-lactamases including AmpC enzymes. A summary of the type of animal models and the beta-lactamases produced by the organisms are described in the table below.

Table 5: Animal Models of Infection Used to Test the Effect of Relebactam on the in Vivo Efficacy of Imipenem

Animal Model	Clinical Isolates (N)	Beta-lactamase	Pathogen	MIC Imipenem (mcg/mL)	MIC Imipenem/REL (mcg/mL)
Murine Delayed Lung	10	PDC 1, 3, 5, 8, 16, 35, 36	*P. aeruginosa*	16-64	4-16
Murine Delayed Lung	2	KPC-2, KPC-3	*K. pneumoniae*	64	0.25-0.05
Murine Thigh	5	PDC 5, 8, 16, 19, 35	*P. aeruginosa*	16-64	≤1-1
Murine Thigh	2	KPC-2, KPC-3	*K. pneumoniae*	2-64	2-16

In the animal models of infection, a reduction in total log10 CFU of the bacterial isolates tested was demonstrated in comparing imipenem versus IMI/REL. As different doses of REL were tested, there was a change in the log10 CFU which indicated a trend towards a dose-dependent effect in the presence of REL. For example, the contribution of REL was shown in the disseminated model of infection with imipenem-resistant *P. aeruginosa* PATOLA 01-08, where there was a change in log10 CFU in the presence of 5 mg/kg imipenem from -0.45 to -3.73 with

the addition of REL (40 mg/kg) and a change in log10 CFU of -1.72 with 10 mg/kg REL. Enhanced in vivo efficacy over imipenem alone in the presence of REL was also seen in the pulmonary infection model with imipenem-resistant *P. aeruginosa* isolates PATOLA 01-08, PATOLA 02-08 and the disseminated model of infection with imipenem-resistant *K. pneumoniae* isolate KLEBTOA 02-08. The contribution of REL was not clearly demonstrated in delayed therapy *P. aeruginosa* lung infection models with PATOLA 04-08, PATOLA 05-08, and BLI-PA-14, however, it is possible that further characterization of the isolates would provide additional insight into the lack of activity against these isolates.

Organisms that were used in the delayed treatment pulmonary models that showed a significant reduction of MIC in the presence of REL included the following examples: *P. aeruginosa* CL5701 which had an imipenem and IMI/REL MIC of 16 mcg/mL and 2 mcg/mL respectively. Also, *K. pneumoniae* isolate 487710 with an imipenem and IMI/REL MIC of 64 mcg/mL and 0.25 mcg/mL respectively; and *K. pneumoniae* isolate 515744 which had an MIC of 64 mcg/mL for imipenem and 0.5 mcg/mL for IMI/REL. The data for the in vivo efficacy studies is provided in the tables of the clinical pharmacology appendix of this review.

Mechanism of Action

Other key aspects of the clinical microbiology review included the establishment of the mechanism of action of REL as an inhibitor of beta-lactamases. This was done primarily through the review of data on enzyme inhibition kinetics of REL on some beta-lactamases such as some members of the following enzyme families: SHV, TEM, CTX-M, P99, *Pseudomonas*-derived cephalosporinase (PDC) and KPCs. The half-maximal inhibitory concentration (IC_{50}) of REL for AmpC was approximately 0.5 µM; the IC_{50} for KPC-2 and KPC-3 was approximately 0.2 µM. Other supportive information was taken from a comparison of the MIC data of imipenem and IMI/REL against bacterial isolates that were genotypically characterized (through methods such as polymerase chain reaction [PCR]) for the presence of beta-lactamases. This included Enterobacteriaceae that produced KPCs and *P. aeruginosa* that produced PDC, a type of AmpC beta-lactamase. IMI/REL was not active against isolates that produced metallo- beta-lactamases, oxacillinases with carbapenemase activity, and certain alleles of GES.

Susceptibility Interpretive Criteria

The Applicant's proposal for breakpoints for Enterobacteriaceae, *P. aeruginosa* and anaerobes was accepted as shown in the table below. The table also reflects the use of 4 mcg/mL REL for MIC susceptibility testing as with other approved beta-lactam, beta-lactamase inhibitor combination products.

Breakpoints for (b) (4) were not established for the following reasons: (b) (4) Footnotes will list the specific Enterobacteriaceae and anaerobes for which efficacy of IMI/REL was demonstrated in clinical trials.

Table 6: Interpretive Criteria for Imipenem-relebactam

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae [a]	≤1/4	2/4	≥4/4	≥25	21-24	≤20
Pseudomonas aeruginosa	≤2/4	4/4	≥8/4	≥23	20-22	≤19
Anaerobes [b,c]	≤4/4	8/4	≥16/4	-	-	-

S = Susceptible; I = Intermediate; R = Resistant

For disk diffusion, use paper disks impregnated with imipenem/relebactam at a concentration of 10/25 mcg/mL.

[a] *Klebsiella aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Klebsiella oxytoca*.

[b] *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides stercoris*, *Bacteroides thetaiotaomicron*, *Fusobacterium nucleatum*, *Parabacteroides distasonis*.

[c] Agar dilution method

4.4 Devices and Companion Diagnostic Issues

There are no devices or companion diagnostics submitted with this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

The product label for IMI lists seizure potential as a warning and precaution and indicates renal adverse events in association with the product. Because nonclinical studies with relebactam revealed a potential for CNS toxicity in rats and renal toxicity in monkeys, it may be important to determine if an additive or synergistic potential for these toxicities can occur when imipenem/cilastatin are clinically administered concomitantly with relebactam.

In 1- and 3-month repeated-dose toxicology studies, relebactam produced only limited toxicity. Two dose-dependent toxicities with clinical relevance were CNS toxicity primarily in rats and minimal kidney toxicity primarily in monkeys. The CNS toxicity in rats variably manifest as decreased activity, sternal recumbency, unsteady gait, intermittent trembling, gasping, and/or convulsions. The CNS effects appeared to be dose-dependent, occurring only with a high 450 mg/kg/day dose of relebactam, but the incidence rates and times to onset in the different studies were inconsistent without a clear explanation for the discrepancies.

In a 7-day exploratory study in rats, no clinical signs were reported in association with repeated daily dosing of intravenous relebactam at a dose of 450 mg/kg/day. In contrast, in the 1-month repeated IV dose study in rats, 2/10 female rats experienced convulsions followed by death after a single high dose of 450 mg/kg relebactam, but none of the other female or male rats in the high-dose group were affected throughout the course of the study. Functional Observational Battery (FOB) measurements on the surviving animals on Day 1 were similar to control values. In the 3-month intravenous-dose study in rats, male and female rats exhibited a range of CNS-related clinical signs in the first 3 days of intravenous dosing with a high-dose of 450 mg/kg/day, but after a dosing holiday on Days 4 and 5 and renewed dosing on Day 6 with a reduced dose of 300 mg/kg/day, clinical signs were no longer observed in high-dose animals.

No CNS-related clinical signs were reported in the 1-month and 3-month toxicology studies in Rhesus monkeys where high daily doses of relebactam were 225 and 150 mg/kg/day respectively. However, in an exploratory rising-dose study with one male and one female Rhesus monkey, the high dose of 225 mg/kg/day relebactam administered for 3 days was associated with transient clinical signs with possible neurological involvement (unsteady gait, trembling, hunched posture, decreased activity, and lateral recumbency) that were observed immediately after each daily dose followed by complete resolution within 25 minutes. In the study report for this study, it was noted that the early batch of relebactam used in this study appeared to undergo degradation over time resulting in the production of an unidentified degradant that may have contributed to the clinical signs. It is not clear if a relebactam

degradant also contributed to the inconsistent CNS toxicity observed in the rat toxicology studies.

The underlying factors contributing to the inconsistent incidence of CNS clinical signs associated with relebactam in rats and monkeys are not clear, but one consistent factor is the dose-dependent nature of the effects. In the rat studies, the 450 mg/kg/day relebactam dose associated with neurological clinical signs produced plasma relebactam exposures approximately 7 times higher than the expected clinical exposures, but NOAEL doses in the rat studies were about 2-fold higher than the expected clinical exposures. No increased signals for relebactam-related CNS effects were observed in clinical studies. CNS adverse events will be monitored during routine post-marketing surveillance.

The primary toxicity in the 1- and 3-month toxicology studies in monkeys was renal toxicity associated with daily IV doses of 150 and 225 mg/kg/day relebactam. In the 1-month study, renal toxicity manifest as increased kidney weights and cytoplasmic granules in renal tubule epithelial cells sometimes accompanied by very slight degeneration of renal tubular epithelium. Complete resolution of the effects was observed after the 1-month recovery period. In the 3-month study which did not include a recovery period, the relebactam dose of 150 mg/kg/day was associated with the same effects but without degeneration of the tubular epithelium.

No kidney effects were observed in the 1-month toxicology study in rats, but cytoplasmic granularity in renal tubular epithelium without evidence of cell degeneration was observed in the 3-month toxicology study in rats. Renal cell granularity was observed for all doses (65, 150, and 450/300 mg/kg/day) in this study, but the severity increased with relebactam dose.

In a 1-month toxicology study in monkeys, the administration of a combination of 37 mg/kg/day relebactam and 150 mg/kg/day imipenem was associated with crystal formation, and slight, transient increases in urinary protein. Imipenem was considered to have predominantly contributed to these findings in that the urinary crystals have been previously linked to imipenem administration in monkeys. Kidney weights were also increased 18% in the group receiving combination therapy with relebactam and imipenem, but this finding was not accompanied by serum chemistry or histopathology correlates.

The relebactam-related kidney toxicity in monkeys and rats, like the CNS toxicity in rats, appears to be dose-related. In the 1-month toxicology study in monkeys, the NOAEL dose for tubular epithelium degeneration was associated with plasma exposures 3.2 to 3.5-fold higher than the expected clinical exposure for relebactam. No increased signals for relebactam-related renal effects were observed in clinical studies. Renal adverse events will be monitored during routine post-marketing surveillance.

In nonclinical pharmacokinetic studies in mice, rats, dogs, and monkeys, IV relebactam plasma exposure increased in a roughly dose-dependent manner, with a plasma $t_{1/2}$ of approximately 1 hour which is similar to the clinical $t_{1/2}$ for both imipenem and cilastatin. Like imipenem,

relebactam was weakly bound by plasma proteins, and did not readily inhibit or induce a broad panel of CYP-450 isozymes suggesting a limited capacity for drug-drug interactions. Relebactam did not demonstrate an ability to interfere with the metabolism or excretion of imipenem and cilastatin. When administered in combination in a one-month toxicology study in monkeys, relebactam, imipenem and cilastatin did not accumulate with repeated-dosing, and none of the compounds altered the plasma exposure or $t_{1/2}$ of the other compounds.

Relebactam was evaluated in a full battery of nonclinical genotoxicity studies. Relebactam was shown to be negative for mutagenicity and/or clastogenic effects in an Ames assay, a chromosomal aberration study, and *in vivo* in a rat bone marrow micronucleus assay. Similarly, according to the imipenem/cilastatin product label, imipenem, cilastatin, and imipenem/cilastatin were shown to be negative for genotoxicity in a V79 mammalian cell mutagenesis assay (imipenem, cilastatin), Ames test (imipenem, cilastatin), unscheduled DNA synthesis assay (imipenem/cilastatin), and *in vivo* in a mouse cytogenetics test (imipenem/cilastatin).

According to the imipenem/cilastatin product label, no adverse effects on fertility, reproductive performance, fetal viability, growth, or postnatal development were observed in male and female rats given imipenem/cilastatin at intravenous doses up to 80 mg/kg/day and at a subcutaneous dose of 320 mg/kg/day. In rats, a dose of 320 mg/kg imipenem was equivalent to approximately double the maximum recommended human dose (MRHD) based on body surface area comparison. Slight decreases in live fetal body weight were reportedly restricted to the highest dosage level. In male and female fertility studies in rats, the highest administered dose of 450 mg/kg/day relebactam did not alter mating performance, fertility, sperm motility, and epididymal sperm counts in male rats or mating performance, fertility, and embryo-fetal survival in female rats. The plasma AUC values associated with the NOAEL dose of 450 mg/kg/day relebactam in the fertility studies were 7.1- (female) and 8.2- (male) times higher than the clinical AUC associated with the MRHD for relebactam.

According to the imipenem/cilastatin product label, embryo-fetal studies with imipenem and cilastatin sodium (alone or in combination) administered to mice, rats, rabbits, and monkeys during the period of organogenesis did not produce fetal malformations at doses equivalent to exposure margins of 0.4 to 5 times the MRHD based on body surface area comparison. However, imipenem-cilastatin sodium administered to monkeys at an intravenous dose of 40 mg/kg/day (approximately 0.4-fold the MRHD based on surface area comparison) caused significant maternal toxicity including death and embryo-fetal loss.
In embryo-fetal studies in mice, rats, and rabbits, the highest administered dose of relebactam (450 mg/kg/day in all studies) was not associated with maternal toxicity or reduced fetal body weights. In rats and rabbits, malformations and variations were not increased by relebactam above concurrent or historical control levels. However, in mice, increases in specific external and/or skeletal alterations were observed. In mice, the sum of all the fetuses/litters affected by any skeletal malformation (skull bone malformation, cervical vertebra malformation, lumbar vertebra malformation, axial skeletal malformation, and absent or extra vertebra) was

increased in the relebactam treatment groups compared to control value with 1/1, 4/4, 3/1, and 5/4 malformed fetuses/litters in the control, low-, mid-, and high-dose groups respectively. Also, the litter incidence of two malformations, cleft palate (15%) and skull bone malformations (15%), in low-dose mice receiving 80 mg/kg/day exceeded the highest litter incidence in the concurrent control group (0% for both cleft palate and skull bone malformation) and in the historical control range (mean of 5.4%; range of 0 - 11% for cleft palate and mean of 0%; range of 0 – 0% for skull bone malformations). Because both cleft palate and skull bone malformations are considered to be rare events, the increased litter incidence of these findings in the low-dose group compared to concurrent and historical control incidences is considered to be drug-related. The results suggest relebactam can increase the incidence of cleft palate and skeletal malformations in mice, and these findings will be described on the product label.

The nonclinical results for relebactam suggest a low potential for clinically relevant adverse events. The two toxicities of concern, CNS toxicity and slight kidney toxicity, both occurred in a dose-dependent manner and overlap with the same broad categories of toxicity associated with clinical administration of imipenem. The potential for additive or synergistic CNS and/or renal adverse events associated with clinical administration of imipenem/cilastatin/ relebactam can be monitored in routine postmarketing surveillance. In embryo-fetal studies, both imipenem/cilastatin and relebactam produced maternal and/or fetal toxicity in some test species suggesting the potential risks should be considered when administering the combination product to pregnant women. Based on the nonclinical results for relebactam and the combination of imipenem/cilastatin and relebactam and the clinically characterized adverse events associated with imipenem administration, the combination product is considered approvable from a Pharmacology/Toxicology perspective.

5.2 Referenced NDAs, BLAs, DMFs

NDA 50587 for PRIMAXIN® (cilastatin sodium; imipenem)

5.3 Pharmacology

Secondary Pharmacology

Relebactam off-target activity was assessed in a large panel of 160 standard enzyme and receptor assays. Relebactam did not demonstrate off-target activity, defined as ≥ 50% inhibition or stimulation at concentrations of ≤ 10 mcM.

Safety Pharmacology

1. **Study Title: Effect of L-002118412-000Z008 on hERG (I_{Kr}), hKCNQ1/hKCNE1 (I_{Ks}), and hNav1.5 (I_{Na}) Currents Stably Expressed in Mammalian Cells. Exploratory Study conducted with PatchXpress 7000A.** (Study No.: TT# 08-3039)

Methods: In this non-GLP compliant study, three cardiac ion channels, hERG, I_{Ks} and I_{Na}, were stably expressed in separate cell preparations of CHO or HEK293 cells and assays of ion channel

function were performed using voltage-clamp technology in the presence of vehicle, and 3, 10, and 30 mcM concentrations of MK-7655.
Results: MK-7655 at the highest test concentration (30 mcM) had no effect on the I_{Ks} potassium currents or I_{Na} sodium currents and hERG potassium channels were inhibited by 2 to 3% with relative to steady state currents with the vehicle.

2. **Study Title: MK-7655: Electrophysiological Evaluation on hERG Channel Current Stably Expressed in CHO Cells.** (Study No.: TT #09-4701)

Methods: In this GLP-compliant study, the effects of two concentrations of MK-7655 (actual concentrations of 32 and 318 mcM) and a positive control (0.03 mcM cisapride) incubated with CHO cells stably transfected with hERG potassium channels were assessed using a patch-clamp technique.
Results: Neither test concentration of MK-7655 inhibited hERG postassium currents to a significant degree. In contrast, cisapride produced a 57.6% inhibition of hERG potassium currents.

3. **Study Title: Ancillary Pharmacology: Effect of MK-7655 on Cardiovascular Function in Anesthetized Dogs.** (Study No.: TT #08-5067)

Methods: In this non-GLP compliant study, MK-7655 was administered intravenously in increasing doses of 3, 7, and 20 mg/kg in three sequential 30-minute infusions to female mongrel dogs. Vehicle was tested in a separate group of dogs. Cardiovascular parameters including blood flow rate, heart rate, mean arterial pressure, and electrocardiogram parameters including PR, QRS, and QT/QTc intervals were monitored during each infusion period.
Results: None of the mean values for the measured cardiovascular parameters changed significantly compared to pretest or control values in the dogs treated with the three concentrations of MK-7655.

4. **Study Title: MK-7655: Intravenous Cardiovascular and Respiratory Telemetry study in Monkeys.** (Study No.: TT #09-5601)

Methods: In this GLP-compliant study, monkeys received intravenous infusions (30 minutes) of the vehicle (0.9% sodium chloride) and 25, 75, and 225 mg/kg of MK-7655 using an ascending dose regimen. Arterial blood pressure (systolic, diastolic and mean blood pressure), heart rate, electrocardiogram parameters (PR, QRS, QT, and QTc), respiratory parameters (rate and depth of respiration), and body temperature were measured for 24 hours after dosing.
Results: No MK-7655-related changes compared to vehicle control values were observed for blood pressure measurements, heart rate, electrocardiogram parameters including QTc intervals, respiratory parameters, or body temperature.

5. **Study title: MK-7655: One Month Intravenous Toxicity Study in Rats with a Functional Observational Battery with a 4-Week Recovery Period**. (Study No.: TT #08-9822

Methods: A functional observational battery (FOB) was conducted in conjunction with the GLP-compliant, 1-month repeated IV toxicology study in rats. The first six male rats in each group were evaluated for CNS function approximately 15 minutes after dosing on Day 1. Observations included: home cage observations, hand-held observations, open field observations, and

stimulus activity responses. Other measured parameters included: forelimb grip strength, hindlimb grip strength, body temperature, foot splay, and hot plate latency.
Results: No MK-7655-related findings were observed for any of the FOB assessments.

5.4 ADME/PK

Type of Study	Major Findings
Absorption	
Pharmacokinetics of MK-7655 in Mouse, Rat, Dog, and Monkey. (Study No.: PK001)	Plasma clearance was approximately 2 times as high in rats as in the other species which had similar clearance. The apparent volume of distribution was similar in all species (0.3-0.4 L/kg) and $t_{1/2}$ values were similar in all groups with a range of 0.5 to 1.2 hours.
Distribution	
***7890In vitro* Metabolism of MK-7655 in Preclinical Species** (Study No.: PK002).	[^{3}H]MK-7655 demonstrated a low, 10-20% capacity, plasma-protein binding in mouse, rat, monkey, and human plasma *in vitro* and preferentially distributed to plasma in blood from the same species.
Quantitative Whole-Body Autoradiography in Male Wistar Hannover and Long-Evans Rats Following a Single 30-Minute Intravenous Infusion Administration of [^{14}C]MK-7655 and Human Dosimetry Prediction. (Study No.: PK005)	The highest concentrations of radioactivity in tissues of male WH rats were found in kidney cortex, kidney medulla, urinary bladder, esophagus, blood, non-pigmented skin, aorta, oral mucosa, lung, and eye uveal tract. Quantifiable radioactivity was not detected in brain, spinal cord, white adipose tissue, and bone. Patterns of distribution in pigmented rats were similar to that observed in albino rats.
Metabolism	
***In vitro* Metabolism of MK-7655 in Preclinical Species** (Study No.: PK002).	Degradation or metabolism of MK-7655 was < 10% and ≤ 3% when incubated with plasma or hepatocytes respectively from several species including human. MK-7655 did not inhibit the enzyme activity of a full panel of CYP-450 isozymes, inhibit the activity of CYP3A4 in a time-dependent manner, or induce the activity of CYP3A4 and CYP1A2.
Excretion	
Excretion of Radioactivity and Plasma Concentration vs. Time Profiles in Intact Rats After Administration of a Single Intravenous Dose of [^{14}C]L-002118412 ([^{14}C]MK-7655). (Study No.: PK010)	The majority of radioactivity was excreted in urine averaging approximately 85% of the administered dose, and a mean value of 8% of the administered dose was excreted in feces.
TK data from general toxicology studies	

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>MK-7655: One-Month Intravenous Toxicity Study in Rats with a Functional Observational Battery with a 4-Week Recovery Period. (Study No.: TT #08-9822)</td><td>
Plasma MK-7655 after 5 Weeks of Dosing
Sex Differences: No substantial sex differences were observed.
$T_{1/2}$: not reported.
Accumulation: Not assessed.
Dose proportionality: The C_{max} values were greater than dose proportional between the 50 and the 150 mg/kg/day dose groups, but approximately dose proportional between the 150 and the 450 mg/kg/day dose groups. The $AUC_{0\text{-}24hr}$ measurements were approximately dose proportional between the 50 and the 150 mg/kg/day dose groups and slightly greater than dose proportional between the 150 and 450 mg/kg/day groups.

Plasma MK-7655 Toxicokinetic Parameters (mean ± SEM) in Rats at the End of Dosing in Week 5. (Table from the Study Report)
<table>
<tr><th>Dose (mg/kg/day)[a]</th><th>Sex</th><th>$AUC_{0\text{-}24\ hr}$ (μM•hr)</th><th>C_{max} (μM)</th><th>T_{max} (hr)</th></tr>
<tr><td>50</td><td>Female</td><td>211 ± 7.16</td><td>511 ± 15.0</td><td>0.050 ± NC</td></tr>
<tr><td></td><td>Male</td><td>263 ± 14.5</td><td>579 ± 15.9</td><td>0.050 ± NC</td></tr>
<tr><td></td><td>All</td><td>237 ± 10.0</td><td>545 ± 16.3</td><td>0.050 ± NC</td></tr>
<tr><td>150</td><td>Female</td><td>747 ± 30.4</td><td>2140 ± 98.9</td><td>0.050 ± NC</td></tr>
<tr><td></td><td>Male</td><td>850 ± 22.3</td><td>2050 ± 88.6</td><td>0.050 ± NC</td></tr>
<tr><td></td><td>All</td><td>798 ± 25.7</td><td>2090 ± 63.6</td><td>0.050 ± NC</td></tr>
<tr><td>450</td><td>Female</td><td>2640 ± 106</td><td>6530 ± 77.7</td><td>0.050 ± NC</td></tr>
<tr><td></td><td>Male</td><td>3040 ± 113</td><td>6440 ± 249</td><td>0.050 ± NC</td></tr>
<tr><td></td><td>All</td><td>2860 ± 91.0</td><td>6480 ± 124</td><td>0.050 ± NC</td></tr>
</table>
[a]Drug concentrations in plasma from all control group animals were below the LLQ of the bioanalytical method.
NC = Not Calculated
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>MK-7655: Three-Month Intravenous Toxicity Study in Rats. (Study No.: TT #16-1003)</td><td>
Plasma MK-7655 after 13 Weeks of Dosing
Sex Differences: No substantial sex differences.
$T_{1/2}$: not reported.
Accumulation: Not conclusively assessed.
Dose proportionality: Mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and C_{max} values of MK-7655 were approximately dose proportional between 65 mg/kg/day and 150 mg/kg/day and less than dose proportional between 150 mg/kg/day and 450/300 mg/kg/day in Study Week 13.

Plasma MK-7655 Toxicokinetic Parameters (mean ± SEM) in Rats Following Dosing of MK-7655 in Week 13. (Table from the Study Report)
<table>
<tr><th>Dose (mg/kg/day)[a]</th><th>Sex</th><th>$AUC_{0\text{-}24\ hr}$ (µM*hr)</th><th>C_{max} (µM)</th><th>T_{max} (hr)</th></tr>
<tr><td>65</td><td>Female</td><td>377 ± 14.9</td><td>744 ± 44.3</td><td>0.080 ± NC</td></tr>
<tr><td></td><td>Male</td><td>449 ± 14.3</td><td>783 ± 75.0</td><td>0.080 ± NC</td></tr>
<tr><td></td><td>All</td><td>413 ± 14.4</td><td>764 ± 40.0</td><td>0.080 ± NC</td></tr>
<tr><td>150</td><td>Female</td><td>825 ± 57.7</td><td>1540 ± 44.7</td><td>0.080 ± NC</td></tr>
<tr><td></td><td>Male</td><td>1020 ± 15.4</td><td>1850 ± 79.7</td><td>0.080 ± NC</td></tr>
<tr><td></td><td>All</td><td>923 ± 36.3</td><td>1690 ± 81.4</td><td>0.080 ± NC</td></tr>
<tr><td>450/300[b]</td><td>Female</td><td>1810 ± 41.0</td><td>3640 ± 158</td><td>0.080 ± NC</td></tr>
<tr><td></td><td>Male</td><td>2220 ± 86.1</td><td>3540 ± 430</td><td>0.080 ± NC</td></tr>
<tr><td></td><td>All</td><td>2010 ± 91.1</td><td>3590 ± 206</td><td>0.080 ± NC</td></tr>
<tr><td colspan="5">NC = Not Calculated
[a]MK-7655 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.0861 µM) of the bioanalytical method.
[b]On study Day 2, the dose level of 450 mg/kg/day was reduced to 300 mg/kg/day.</td></tr>
</table>
</td></tr>
<tr><td>MK-7655: One-month Intravenous Toxicity Study in Monkeys with a 4-week Recovery Period. (Study No.: TT #08-1153)</td><td>
Plasma MK-7655 after 1 Day and 4 Weeks of Dosing
Sex Differences: No substantial sex differences were observed.
$T_{1/2}$: not reported.
Accumulation: MK-7655 did not accumulate in plasma with repeated-dosing.
Dose proportionality: MK-7655 C_{max} values increased in a dose-proportional manner on both Day 1 and Week 4, and $AUC_{0\text{-}24h}$ values increased in a dose-proportional or slightly greater than dose-proportional manner.

Plasma MK-7655 Toxicokinetic Parameters in Monkeys Following Dosing of MK-7655 on Study Day 1 and Study Week 4. (Table from the Study Report)
<table>
<tr><th></th><th colspan="3">MK-7655 (mg/kg/day)[a]
Sexes Combined</th></tr>
<tr><th></th><th>25</th><th>75</th><th>225</th></tr>
<tr><td>Study Day 1</td><td></td><td></td><td></td></tr>
<tr><td>$AUC_{0\text{-}24\ hr}$ (µM•hr)</td><td>288 ± 8.89</td><td>902 ± 49.1</td><td>4080 ± 639</td></tr>
<tr><td>C_{max} (µM)</td><td>472 ± 8.47</td><td>1280 ± 128</td><td>4500 ± 114</td></tr>
<tr><td>T_{max} (hr)</td><td>0.017 ± 0.0</td><td>0.056 ± 0.039</td><td>0.017 ± 0.0</td></tr>
<tr><td>Study Week 4</td><td></td><td></td><td></td></tr>
<tr><td>$AUC_{0\text{-}24\ hr}$ (µM•hr)</td><td>213 ± 13.9</td><td>666 ± 29.2</td><td>2610 ± 74.2</td></tr>
<tr><td>C_{max} (µM)</td><td>341 ± 30.4</td><td>1160 ± 47.8</td><td>3570 ± 73.5</td></tr>
<tr><td>T_{max} (hr)</td><td>0.017 ± 0.0</td><td>0.017 ± 0.0</td><td>0.017 ± 0.0</td></tr>
<tr><td colspan="4">Values are the mean ± SEM.
[a] Drug concentrations in plasma from all control group animals were below the LLQ of the bioanalytical Method.</td></tr>
</table>
</td></tr>
</table>

Type of Study	Major Findings
MK-7655: Three-Month Intravenous Toxicity Study in Rhesus Monkeys. (Study No.: TT #14-1089)	**Plasma MK-7655 after 1 Day and 13 Weeks of Dosing** Sex Differences: No substantial sex differences were observed. $T_{1/2}$: not reported. Accumulation: MK-7655 did not accumulate in plasma with repeated daily dosing for 13 weeks. Dose proportionality: The mean $AUC_{0\text{-}24\ hr}$ and C_{max} values for plasma MK-7655 increased in an approximately dose-proportional manner across the three dose groups on both Study Day 1 and in Study Week 13. **Plasma MK-7655 Toxicokinetic Parameters (mean ± SEM) on Day 1 and Week 13 of the 3-Month Toxicology Study in Monkeys.** (Table from the Study Report)

Day	Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (μM*hr)	C_{max} (μM)	T_{max} (hr)
1	25	Female	254 ± 9.25	320 ± 23.6	0.017 ± 0.0
		Male	277 ± 15.3	373 ± 30.4	0.017 ± 0.0
		All	265 ± 9.38	347 ± 20.4	0.017 ± 0.0
	50	Female	549 ± 39.6	675 ± 74.9	0.017 ± 0.0
		Male	581 ± 47.0	654 ± 62.2	0.017 ± 0.0
		All	565 ± 29.1	665 ± 45.2	0.017 ± 0.0
	150	Female	1770 ± 23.7	1980 ± 112	0.075 ± 0.058
		Male	1720 ± 78.8	2100 ± 200	0.017 ± 0.0
		All	1740 ± 39.3	2040 ± 109	0.046 ± 0.029

Week	Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (μM*hr)	C_{max} (μM)	T_{max} (hr)
13	25	Female	264 ± 46.0	392 ± 37.1	0.017 ± 0.0
		Male	191 ± 5.20	369 ± 25.6	0.017 ± 0.0
		All	227 ± 25.4	380 ± 21.3	0.017 ± 0.0
	50	Female	373 ± 11.3	765 ± 45.3	0.017 ± 0.0
		Male	399 ± 12.0	734 ± 41.8	0.017 ± 0.0
		All	386 ± 9.05	749 ± 29.1	0.017 ± 0.0
	150	Female	1350 ± 60.9	2380 ± 76.3	0.017 ± 0.0
		Male	1250 ± 115	2310 ± 53.3	0.017 ± 0.0
		All	1300 ± 62.9	2340 ± 45.2	0.017 ± 0.0

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>MK-7655: One-Month Intravenous/Subcutaneous Toxicity Study in Rhesus Monkeys. (Study No.: TT #09-1124)</td><td>
Plasma MK-7655, Imipenem, and Cilastatin on Day 1 and Week4 of Dosing
Sex Differences: No substantial sex differences were observed for plasma AUC and C_{max} measurements of imipenem, cilastatin, and MK-7655.
$T_{1/2}$: not reported.
Accumulation: None of the test compounds, imipenem, cilastatin, or MK-7655 accumulated in plasma with repeated daily dosing for 31 days.
Dose proportionality: Not assessed.

Plasma Toxicokinetic Parameters (mean ± SEM) for MK-7655, Imipenem, and Cilastatin on Day 1 and Week 4 of the 1-Month Combination Toxicology Study in Monkeys. (Table from the Study Report)
<table>
<tr><th></th><th>$AUC_{0\text{-}24hr}$ (µM x hr)</th><th>C_{max} (µM)</th></tr>
<tr><td>Day 1</td><td></td><td></td></tr>
<tr><td>MK-7655</td><td>575 ± 69.7</td><td>692 ± 25.7</td></tr>
<tr><td>Imipenem</td><td>1680 ± 190</td><td>948 ± 43.5</td></tr>
<tr><td>Cilastatin</td><td>955 ± 146</td><td>722 ± 42.6</td></tr>
<tr><td>Week 4</td><td></td><td></td></tr>
<tr><td>MK-7655</td><td>447 ± 30.2</td><td>664 ± 68.4</td></tr>
<tr><td>Imipenem</td><td>1590 ± 88.9</td><td>1080 ± 56.2</td></tr>
<tr><td>Cilastatin</td><td>747 ± 45.8</td><td>756 ± 35.4</td></tr>
</table>
</td></tr>
<tr><td colspan="2">TK data from reproductive toxicology studies</td></tr>
<tr><td>MK-7655: Intravenous Fertility and Toxicokinetic Study in Male Rats. (Study No.: TT #12-7410)</td><td>
Plasma Toxicokinetic Parameters (mean ± SEM) for MK-7655 in the Male Fertility Study in Rats on Day 1. (Table from the Study Report)
<table>
<tr><th>Dose (mg/kg)</th><th>$AUC_{0\text{-}24\ hr}$ (µM•hr)</th><th>C_{max} (µM)</th><th>T_{max} (hr)</th></tr>
<tr><td>50</td><td>285 ± 32.0</td><td>397 ± 125</td><td>0.050 ± NC</td></tr>
<tr><td>150</td><td>986 ± 24.5</td><td>1490 ± 26.9</td><td>0.050 ± NC</td></tr>
<tr><td>450</td><td>3210 ± 164</td><td>4680 ± 358</td><td>0.050 ± NC</td></tr>
</table>
NC = Not Calculated
</td></tr>
<tr><td>MK-7655: Intravenous Fertility and Toxicokinetic Study in Female Rats. (Study No.: TT #12-7400)</td><td>
Plasma Toxicokinetic Parameters (mean ± SEM) for MK-7655 in the Female Fertility Study in Rats on Day 1. (Table from the Study Report)
<table>
<tr><th>Dose (mg/kg)</th><th>$AUC_{0\text{-}24\ hr}$ (µM•hr)</th><th>C_{max} (µM)</th><th>T_{max} (hr)</th></tr>
<tr><td>50</td><td>272 ± 11.0</td><td>591 ± 22.8</td><td>0.050 ± NC</td></tr>
<tr><td>150</td><td>892 ± 26.9</td><td>1720 ± 36.2</td><td>0.050 ± NC</td></tr>
<tr><td>450</td><td>2780 ± 91.9</td><td>5680 ± 301</td><td>0.050 ± NC</td></tr>
</table>
NC = Not Calculated
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>MK-7655: Subcutaneous Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Mice. (Study No.: TT #12-7330)</td><td>Plasma MK-7655 Toxicokinetic Parameters (mean ± SEM) for MK-7655 in Pregnant Mice on Gestation Day 13. (Table from the Study Report)
<table>
<tr><th>Dose (mg/kg/day)[a]</th><th>$AUC_{0\text{-}24\ hr}$ (μM•hr)</th><th>C_{max} (μM)</th><th>T_{max} (hr)</th></tr>
<tr><td>80</td><td>493 ± 27.9</td><td>297 ± 20.1</td><td>0.33 ± NC</td></tr>
<tr><td>200</td><td>1070 ± 58.5</td><td>654 ± 45.2</td><td>0.083 ± NC</td></tr>
<tr><td>450</td><td>2220 ± 89.7</td><td>1500 ± 112</td><td>0.083 ± NC</td></tr>
</table>
NC = Not Calculated
[a] MK-7655 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.086 μM) of the bioanalytical method.</td></tr>
<tr><td>MK-7655: Intravenous Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats. (Study No.: TT #12-7320)</td><td>Plasma MK-7655 Toxicokinetic Parameters (mean ± SEM) for MK-7655 in Pregnant Rats on Gestation Day 15. (Table from the Study Report)
<table>
<tr><th>Dose (mg/kg/day)</th><th>$AUC_{0\text{-}24\ hr}$ (μM•hr)</th><th>C_{max} (μM)</th><th>T_{max} (hr)</th></tr>
<tr><td>50</td><td>255 ± 9.08</td><td>420 ± 116</td><td>0.050 ± NC</td></tr>
<tr><td>150</td><td>761 ± 62.0</td><td>1590 ± 101</td><td>0.050 ± NC</td></tr>
<tr><td>450</td><td>2800 ± 161</td><td>5440 ± 402</td><td>0.050 ± NC</td></tr>
</table>
NC = Not Calculated
[a] MK-7655 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.086 μM) of the bioanalytical method.</td></tr>
<tr><td>MK-7655: Intravenous Embryo-Fetal Developmental Toxicity Study in Rabbits. (Study No.: TT #15-7200)</td><td>Plasma Toxicokinetic Parameters (mean ± SEM) for MK-7655 in Pregnant Rabbits on Gestation Day 15. (Table from the Study Report)
<table>
<tr><th>Dose (mg/kg/day)[a]</th><th>$AUC_{0\text{-}24\ hr}$ (μM*hr)</th><th>C_{max} (μM)</th><th>T_{max} (hr)</th></tr>
<tr><td>35</td><td>427 ± 16.0</td><td>560 ± 33.8</td><td>0.050 ± 0.0</td></tr>
<tr><td>275</td><td>4540 ± 329</td><td>3910 ± 77.0</td><td>0.050 ± 0.0</td></tr>
<tr><td>450</td><td>9490 ± 610</td><td>7200 ± 302</td><td>0.050 ± 0.0</td></tr>
<tr><td colspan="4">a MK-7655 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.0861 μM) of the bioanalytical method.</td></tr>
</table></td></tr>
<tr><td>MK-7655: Intravenous Pre- and Postnatal Developmental Toxicity Study in Rats. (Study No.: TT #15-7050)</td><td>Plasma Toxicokinetic Parameters (mean ± SEM) for MK-7655 Following IV Dosing to Pregnant Rats on Gestation Day 15 in the Pre- Postnatal Study. (Table from the Study Report)
<table>
<tr><th>Dose (mg/kg/day)</th><th>Sex</th><th>$AUC_{0\text{-}24\ hr}$ (μM*hr)</th><th>C_{max} (μM)</th><th>T_{max} (hr)</th></tr>
<tr><td>65</td><td>Female</td><td>393 ± 10.3</td><td>771 ± 17.7</td><td>0.050 ± 0.0</td></tr>
<tr><td>200</td><td></td><td>1360 ± 85.1</td><td>2220 ± 52.6</td><td>0.050 ± 0.0</td></tr>
<tr><td>450</td><td></td><td>3020 ± 62.3</td><td>5380 ± 101</td><td>0.050 ± 0.0</td></tr>
</table></td></tr>
</table>

5.5 Toxicology

5.5.1 General Toxicology

Imipenem/Cilastatin: Several clinical adverse reactions have been observed to occur with an incidence of ≥ 0.2% of patients receiving PRIMAXIN® as noted on the 2018 product label.

- CNS adverse reactions including seizures and other CNS adverse experiences, such as confusional states and myoclonic activity, have been reported during treatment with PRIMAXIN®, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Convulsions were also reported with a 5.9% incidence with the administration of PRIMAXIN® to neonatal patients and infants up to 3 months of age.
- Renal adverse reactions including oliguria/anuria and polyuria are reported as occurring with an incidence of less than 0.2% in patients receiving PRIMAXIN® since its approval. Also, the label identifies adverse laboratory changes including increased blood urea nitrogen (BUN), creatinine, and the presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen. In clinical trials with pediatric patients less than 3 months of age, oliguria/anuria was reported with an incidence of 2.2%.

Relebactam: repeated-dose toxicology studies with MK-7655 are summarized or reviewed below.

Study title/ number: MK-7655: Three-Month Intravenous Toxicity Study in Rats. /TT #16-1003

- High-dose rats receiving intravenous doses of 450 mg/kg/day MK-7655 exhibited CNS-related clinical signs including decreased activity, sternal recumbency, unsteady gait, convulsion-like activity (rolling), intermittent trembling, gasping, rapid breathing, and red discoloration in ears. After a reduction of the high dose to 300 mg/kg/day on the second day of dosing, CNS-related clinical signs entirely subsided by Day 6.
- Cytoplasmic granularity was observed in the renal tubular epithelium at all MK-7655 dose levels. Severity of the cytoplasmic granularity was minimal at 65 mg/kg/day and mild at 150 mg/kg/day and 450/300 mg/kg/day. The cytoplasmic granularity was characterized by the presence of numerous small, fine, distinct, round eosinophilic granules distributed within the cytoplasm of renal tubular epithelial cells in the cortex. No evidence of renal necrotic or degenerative changes or alterations in urinalysis parameters or blood urea nitrogen (BUN) or serum creatinine was observed in these rats.
- Because of the CNS effects in the high-dose rats, the NOAEL dose was considered to be the mid-dose of 150 mg/kg/day.

Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, Pennsylvania, USA
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (Group 1), 65 (Group 2), 150 (Group 3), and 450/300 mg/kg/day (Group 4) administered once per day
Route of administration:	Intravenous via tail vein
Formulation/Vehicle:	0.9% Sodium Chloride in Water for Injection
Species/Strain:	Rat/Wistar Han, Crl:WI(Han)
Number/Sex/Group:	12/sex/group for Groups 1-3 and 16/sex/group for Group 4
Age:	11 weeks
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	On Day 2, one HD female receiving 450 mg/kg/day was found dead prior to dosing. On Day 3 another HD female was euthanized in extremis. Both animals exhibited clinical signs as described below. In response to the first death, the dose level for the high dose group receiving 450 mg/kg/day was reduced to 300 mg/kg/day on Study Days 2 and 3 and from Study Day 6 until study termination, with a dosing holiday on Study Days 4 and 5.
Clinical Signs	On Day 1, the HD female that was found dead on Day 2 exhibited clinical signs including decreased activity, sternal recumbency, unsteady gait, convulsion-like activity (rolling), rapid breathing, and red discoloration in ears. The HD female that was euthanized in extremis on Day 3 exhibited decreased activity, sternal recumbency, red ears and unsteady gate on Day 1, red ears on Day 2, and self-mutilation, intermittent whole-body trembling, convulsion-like activity, and intermittent gasping on Day 3 before euthanasia. Additional clinical signs in HD animals in the six days of dosing included red discoloration of ears in all high-dose animals, decreased activity, sternal recumbency in most males and females and gasping in intermittent vocalization in one female. Lower dose animals were not similarly affected and all clinical signs in HD animals resolved after Day 6.
Body Weights	Body weights were not significantly reduced in any of the MK-7655 dose groups compared to control animals.
Ophthalmoscopy	No MK-7655-related ophthalmic findings were observed.

Hematology	Compared to control mean values in Study Week 4, hematology changes in the HD female that was euthanized in extremis on Day 3 consisted of increased reticulocyte counts with increased mean corpuscular volume and decreased mean cell hemoglobin and mean cell hemoglobin concentration. Increased activated partial thromboplastin time was present. Increased white blood cell counts in this animal was associated with increased lymphocyte and monocyte counts. However, the hematology changes were observed only in the HD animal that was euthanized in extremis, and not in the remaining HD animals or animals in the other MK-7655 dose groups.
Clinical Chemistry	In the single HD female euthanized in extremis on Day 3, blood urea nitrogen, creatinine, potassium and phosphorus concentrations were increased as well as aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase activities compared to control values in Week 12. However, no significant changes were observed in any of the surviving HD animals or in animals in the LD and MD MK-7655 groups.
Urinalysis *[delete the row if not evaluated]*	No changes in any of the urinalysis parameters were observed for any of the MK-7655 dose groups compared to control values.
Gross Pathology	No unusual gross pathology findings were observed.
Organ Weights	None of the absolute or relative organ weights were significantly changed in the MK-7655 treatment groups compared to vehicle control values.
Histopathology Adequate battery: Yes	The only MK-7655-related histopathology finding in the high-dose animals that survived until the scheduled termination date was cytoplasmic granularity observed in the renal tubular epithelium at all MK-7655 dose levels. Severity of the cytoplasmic granularity was minimal at 65 mg/kg/day and mild at 150 mg/kg/day and 450/300 mg/kg/day. The cytoplasmic granularity was characterized by the presence of numerous small, fine, distinct, round eosinophilic granules distributed within the cytoplasm of renal tubular epithelial cells in the cortex. There was no evidence of necrotic or degenerative changes or any other form of renal injury in the kidneys associated with the eosinophilic granules in the renal tubular epithelial cells at any dose level. There were also no MK-7655-related alterations in urinalysis parameters or blood urea nitrogen (BUN) or serum creatinine in these rats.
[Other evaluations]	None

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.
*: *[if the answer is "no" explain why the histopath battery is not adequate]*

Study title/ number: MK-7655: Three-Month Intravenous Toxicity Study in Rhesus Monkeys. / TT #14-1089

- The only MK-7655-related histopathology finding was the minimal to mild cytoplasmic nongranularity observed in the renal tubular epithelium of all the monkeys in the high-dose group (150 mg/kg/day). This was characterized by the presence of numerous small distinct round eosinophilic granules distributed within the cytoplasm. There were no associated findings of renal tubular epithelial degeneration or changes in any renal function parameters in the urinalysis and serum chemistry evaluations.
- Because the eosinophilic staining in the kidney was not associated with clear

structural or functional changes indicative of kidney toxicity, the NOAEL was considered to be the high-dose of 150 mg/kg/day.

Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, Pennsylvania, 19486
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (Group 1), 25 (Group 2), 50 (Group 3), and 150 mg/kg/day (Group 4) administered once per day
Route of administration:	Intravenous via the saphenous veins. Each infusion was delivered over approximately 4 minutes
Formulation/Vehicle:	0.9% Sodium Chloride in Water for Injection, USP
Species/Strain:	Monkey/Rhesus
Number/Sex/Group:	4/sex/group
Age:	Males: 2.5 to 4.2 kg; Females: 2.3 to 4.2 kg
Satellite groups/ unique design:	No satellite groups/ A recovery study was not included.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No unscheduled deaths occurred.
Clinical Signs	Intermittent, low incidence, red discoloration at injection sites were observed in all groups including the control group, but no MK-7655-related clinical signs were observed.
Body Weights	No MK-7655-related changes in body weights occurred.
Ophthalmoscopy	No MK-7655-related ophthalmic changes were observed.
ECG *[delete the row for rodents]*	No MK-7655-related changes in heart rate or ECG intervals were observed.
Hematology	None of the evaluated hematology or coagulation parameters changed in a MK-7655-dependent manner.
Clinical Chemistry	None of the evaluated serum chemistry parameters were altered in a MK-7655-dependent manner.
Urinalysis *[delete the row if not evaluated]*	No MK-7655-related changes occurred in the measured urinalysis parameters.
Gross Pathology	No MK-7655-related gross pathology was observed.
Organ Weights	No absolute or relative organ weights were significantly changed compared to negative control values.

Histopathology Adequate battery: Yes	The only MK-7655-related histopathology finding was the minimal to mild cytoplasmic nongranularity observed in the renal tubular epithelium of all the monkeys in the HD group (150 mg/kg/day). This was characterized by the presence of numerous small distinct round eosinophilic granules distributed within the cytoplasm. There was no associated evidence of renal tubular epithelial degeneration or any other form of renal injury in high-dose animals. Kidneys of monkeys in the LD and MD groups were not similarly affected.
[Other evaluations]	None

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.
*: *[if the answer is "no" explain why the histopath battery is not adequate]*

General toxicology; additional studies

1. **MK-7655: One-month intravenous toxicity study in rats with a functional observational battery with a 4-week recovery period/ TT #08-9822**

Methods: In a GLP-compliant study, male and female Wistar Hanover Rats (10/sex/group) were administered vehicle (Group 1: 0.9% sodium chloride) or 50 (Group 2), 150 (Group 3), and 450 (Group 4) mg/kg/day MK-7655 daily by intravenous administration for 4 weeks. In Groups 1 and 4, the first 9-10 rats/sex/group were used for the Main Study necropsy in Week 5, and the last 4-5 rats/sex/ group were used for the Recovery necropsy in Week 9. For Groups 2 and 3, all rats were necropsied in Week 5 for the Main Study.

Results: In surviving animals, daily intravenous administration of MK-7655 at doses as high as 450 mg/kg/day did not produce any apparent toxicity in the form of clinical signs, gross pathology, histopathology or altered hematology, clinical chemistry, ophthalmology and organ weights. However, two females in the high-dose group experienced convulsions and died following the first dose. The NOAEL for this study was considered to be 150 mg/kg/day for females and 450 mg/kg/day for males.

2. **MK-7655: One-month Intravenous Toxicity Study in Monkeys with a 4-week Recovery Period/ TT #08-1153**

Methods: In a GLP-compliant study, male and female Rhesus Monkeys (3/sex/group) were administered vehicle (Group 1: 0.9% sodium chloride) or 25 (Group 2), 75 (Group 3), and 225 (Group 4) mg/kg/day MK-7655 daily by intravenous administration for 31 days before necropsy. Additional recovery animals (2/sex/group) in Groups 1 and 4 were dosed for 31 days, then maintained without dosing for an additional 4 weeks before necropsy.

Results: Intravenous administration of MK-7655 for one month resulted in a 36% increase in kidney weight in the high-dose group which correlated with very slight to slight granularity in kidney tubule epithelial cells in 6/6 high-dose animals, and renal tubule epithelial degeneration in 2/6 high-dose animals. The kidney weights and epithelial granularity and degeneration resolved following the recovery period as did slight (≤ 10%) decreases in erythrocyte numbers,

hemoglobin, and hematocrit in high-dose males and females. One animal in the medium-dose group (75 mg/kg/day) also demonstrated cytoplasmic granularity in renal tubule epithelial cells but without cellular degeneration. The NOAEL for this study was considered to be 75 mg/kg/day.

3. MK-7655: Exploratory One-Month Intravenous and Subcutaneous Toxicity Study in Rabbits/ TT #15-7060

Methods: In this non-GLP study, New Zealand White rabbits (3-4/sex/group) were administered vehicle (0.9% sodium chloride) by the intravenous (IV) route (Group 1) and subcutaneous (SC) route (Group 2) or IV 240 mg/kg/day MK-7655 (Group 3), SC 75 mg/kg/day MK-7655 (Group 4), and SC 240 mg/kg/day MK-7655 (Group 5) for 31 days. All animals were necropsied on Day 32. Only the brain and kidneys were weighed at necropsy and only the kidney was examined for histopathology.

Results: The only MK-7655-related finding was discolored urine with brown and/or white precipitate that was observed in male and female rabbits receiving IV and SC 240 mg/kg/day MK-7655 and at a lower incidence in rabbits receiving IV 75 mg/kg/day MK-7655. The applicant speculated that the urine precipitates may have been associated with excretion of a MK-7655 hydrolysis product. No kidney histopathology findings or functional kidney changes were observed suggesting the discolored urine was not toxicologically relevant. The study was deficient in the limited panel of organs that were examined for organ weights and histopathology in the MK-7655 treatment groups.

4. MK-7655: One-month intravenous/subcutaneous toxicity study in Rhesus Monkeys/ TT #09-1124

Methods: Rhesus monkeys (3/sex/group) were administered intravenous MK-7655 (37.5 mg/kg/day) plus PRIMAXIN® (imipenem/cilastatin: 30 mg/kg/day intravenous plus 120 mg/kg/day subcutaneous) for 31 days followed by necropsy on Day 32.

Results: Monkeys demonstrated test article-related changes in physical signs (liquid/unformed feces, discolored urine, and post-dose salivation) as well as urinalysis changes (presence of trichomonas crystals and slightly increased protein concentration). The urinalysis changes were not accompanied by correlating serum chemistry alterations or histopathology indicative of kidney toxicity. The Applicant reported that crystals similar to those in the current study had previously been observed in a monkey study using PRIMAXIN® alone.

5.5.2 Genetic Toxicology

Imipenem/Cilastatin: The 2018 product label for PRIMAXIN® (imipenem and cilastatin) for Injection includes the following information regarding the genetic toxicology of imipenem and cilastatin: "A variety of bacterial and mammalian tests were performed to evaluate genetic

toxicity. The tests used were: V79 mammalian cell mutagenesis assay (cilastatin sodium alone and imipenem alone), Ames test (cilastatin sodium alone and imipenem alone), unscheduled DNA synthesis assay (imipenem/cilastatin sodium) and *in vivo* mouse cytogenetics test (imipenem/cilastatin sodium). None of these tests showed any evidence of genetic alterations."

Relebactam: The genetic toxicology studies with relebactam (MK-7655) are reviewed below.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: MK-7655: Microbial Mutagenesis Assay/ TT #09-8003, TT #09-8012, and TT #09-8016

Key Study Findings:

- In two separate assays and a repeat assay, MK-7655 at concentrations of ≤ 3000 µg/plate, with and without metabolic activation, did not produce a 2-fold increase in the number of revertant colonies or a dose-related increase in the number of revertant colonies. Thus, MK-7655 was not considered mutagenic in the Ames assay.

GLP compliance: Yes

Test system: *Salmonella typhimurium*: TA1535, TA97a, TA98, and TA100 and *Escherichia coli*: WP2 uvrA pKM101

Study is valid: Yes. The criteria for study validity were not directly addressed in the study report. However, the Sponsor indicated that the negative control plates for each test strain fell within historical ranges, except where noted in the first definitive study (TT #09-8012). Also, 2-aminoanthracene (the positive control) and the diagnostic mutagens consistently produced 2-fold or greater increases in revertant frequency in appropriate strains under appropriate conditions. Therefore, except where noted for assay TT #09-8012, the study was considered valid.

In Vitro Assays in Mammalian Cells

Study title/ number: MK-7655: Assay for Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells/ TT #09-8604, TT #09-8608, TT #09-8614

Key Study Findings:

- MK-7655, at concentrations as high as 10 mM, was negative for chromosomal aberrations in CHO cells in culture conditions with and without metabolic activation.

GLP compliance: Yes

Test system: Chinese hamster ovary cells, subclone WBL

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: MK-7655: Assay for Micronucleus Induction in Rat Bone Marrow from a 1-month Intravenous Toxicity Study/ TT #08-8809

Key Study Findings:

- The assay of MK-7655 for micronucleus induction in bone marrow was negative in female and male rats after daily intravenous treatment with doses of 50, 150, and 450 mg/kg/day for approximately one month.

GLP compliance: Yes
Test system: Crl:WI(HAN) rats
Study is valid: Yes

Other Genetic Toxicity Studies
No other genetic toxicology studies for relebactam, imipenem, or cilastatin were submitted with the NDA 212819 application.

5.5.3 Carcinogenicity

No carcinogenicity studies were conducted.

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Imipenem/Cilastatin: Regarding fertility, the information included on the PRIMAXIN® product label is as follows: "Reproductive tests in male and female rats were performed with imipenem-cilastatin sodium at intravenous doses up to 80 mg/kg/day and at a subcutaneous dose of 320 mg/kg/day, 2.1 times the maximum recommended daily human dose of the intramuscular formulation (on a mg/m2 body surface area basis). Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups."

Relebactam: Study reports for MK-7655 (relebactam) fertility studies in male and female rats are reviewed below.

Study title/ number: Intravenous Fertility and Toxicokinetic Study in Male Rats./ TT #12-7410
Key Study Findings

- Other than a transient, MK-7655-related, decrease in mean body weight gain in high-dose males during the premating period, there was no other evidence of general toxicity in this group or in the lower dose groups.
- There was no MK-7655-related reproductive toxicity at any dose level as assessed by mating performance, fertility, embryo/fetal survival parameters, and sperm analysis.
- The NOAEL for male fertility parameters in rats was considered to be the high dose of 450 mg/kg/day which was associated with plasma C_{max} and AUC values of 4680 mcM and 3210 mcM•hr respectively and an 8.2-fold exposure margin compared to the maximum recommended human dose for relebactam based on AUC comparison.

Conducting laboratory and location:	Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, West Point, Pennsylvania
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 50, 150, and 450 mg/kg/day administered once per day
Route of administration:	Intravenous via tail vein
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Rat/Sprague Dawley, Crl:CD(SD)
Number/Sex/Group:	20 males/group
Satellite groups:	Toxicokinetic animals: 4 males in the control group and 8 animals for each of the MK-7655 groups.
Study design:	Males were administered vehicle or different doses of MK-7655 beginning 15 days prior to cohabitation, during cohabitation, and until Day 1 prior to the scheduled sacrifice for a total of approximately 6 weeks of dosing. For mating and fertility assessments, males were housed with untreated females following 15 days of treatment. The cohabitation interval was limited to a maximum of 10 nights. Mating was confirmed by daily examination of females for copulatory plugs. The day of confirmed mating was considered to be gestation day (GD)0. Between GD15 and 17, all pregnant females were euthanized and uterine contents were examined. Plasma MK-7655 concentrations were determined after a single dose in non-fasted control and MK-7655-treated males.
Deviation from study protocol affecting interpretation of results:	No

Reviewer Comment: *The period of dosing before mating for males was shorter than is recommended by the ICH S5A Guidance which recommends dosing for at least 4 weeks in the premating period for males. It is not clear if the reduced duration of dosing in males altered the spermatogenesis results or other fertility parameters.*

Observations and Results

Parameters	Major findings
Mortality	No premature animal deaths occurred.
Clinical Signs	No clinical signs were observed in male rats.
Body Weights	In high-dose males, there was a transient MK-7655-related decrease in mean body weight gain in the premating period between Study Weeks 1 and 3 (26% below control). Thereafter, mean body weight gains in the 450 mg/kg/day group were comparable to concurrent control.

Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]*	There were no MK-7655-related effects on mating performance and fertility. In the MK-7655 groups, mean values for mating index (percent of mated females/females cohabited), fecundity index (percent of pregnant females/mated females), and fertility index (percent of pregnant females/females cohabited) were similar to those seen in the control group. Epididymal sperm analysis did not reveal any MK-7655-related changes in sperm counts or sperm motility.

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: MK-7655: Intravenous Fertility and Toxicokinetic Study in Female Rats/ TT #12-7400

Key Study Findings

- There was no MK-7655-related reproductive toxicity as assessed by mating performance, fertility, and embryonic-fetal survival parameters.
- The NOAEL for rat female fertility parameters was considered to be the high dose of 450 mg/kg/day which was associated with plasma C_{max} and AUC values of 5680 mcM and 2780 mcM•hr respectively and a 7.1-fold exposure margin compared to the maximum recommended human dose for relebactam based on AUC comparison.

Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, West Point, Pennsylvania

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 50, 150, and 450 mg/kg/day administered once daily

Route of administration: Intravenous via tail vein

Formulation/Vehicle: 0.9% sodium chloride injection

Species/Strain: Rat/Sprague-Dawley, Crl:CD(SD)

Number/Sex/Group: 20 females/group

Satellite groups: 4 females in the control group and 8 females/MK-7655 treatment group were designated for toxicokinetic analysis.

Study design: Females received intravenous injections of vehicle or MK-7655 (50, 150, and 450 mg/kg/day) beginning 15 days prior to cohabitation, during cohabitation, and through gestation day (GD) 7. Each female was housed with 1 untreated male of the same strain on the afternoon of premating day (PMD) 15. On GD 15 to 17 surviving females were euthanized, and uterine contents were examined. Mating performance and fertility were also assessed, and plasma toxicokinetics for MK-7655 were

	performed in toxicokinetic females (non-fasted and non-pregnant) after a single dose of vehicle or test item.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	All MK-7655-treated animals survived until the scheduled termination. One control female was found dead on PMD 8 immediately after dosing. The cause of death was not determined.
Clinical Signs	No MK-7655-related clinical signs were observed.
Body Weights	No MK-7655-related changes in body weight were observed.
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]*	Mating performance and fertility were not affected by MK-7655 at any dose. The number of pregnant females, and matings per 4-day periods of cohabitation, and the mating, fecundity and fertility indexes were similar in all groups. Also, no MK-7655-related changes in any of the Caesarean section data including the number of corpora lutea, implantations, resorptions, and live fetuses per female were observed.

LD: low dose; MD: mid dose; HD: high dose

Embryo-Fetal Development

Imipenem/Cilastatin: Regarding embryo-fetal effects the information included on the 2018 PRIMAXIN® product label is as follows: "Reproductive toxicity studies with imipenem and cilastatin (alone or in combination) administered to mice, rats, and rabbits showed no evidence of effects on embryofetal (mice, rats and rabbits) or pre/postnatal (rats) development.

Imipenem was administered intravenously to rats (gestation days (GD) 7 to 17) and rabbits (GD 6 to 18) at doses up to 900 and 60 mg/kg/day, respectively, approximately 2.9 and 0.4 times the RHD (based on body surface area).

Cilastatin was administered subcutaneously to rats (GD 6 to 17) and intravenously to rabbits (GD 6 to 18) at doses up to 1000 and 300 mg/kg/day, respectively, approximately 3.2 and 1.9 times the RHD (based on body surface area).

Imipenem/cilastatin was administered intravenously to mice at doses up to 320 mg/kg/day (GD 6 to 15). In two separate studies, imipenem/cilastatin was administered to rats (GD 6 to 17 and GD 15 to day 21 postpartum) both intravenously at doses up to 80 mg/kg/day and subcutaneously at 320 mg/kg/day. The higher dose is approximately equal to the RHD (based on body surface area).

Imipenem/cilastatin administered intravenously to pregnant cynomolgus monkeys during organogenesis at 100 mg/kg/day, approximately 0.6 times the RHD (based on body surface area), at an infusion rate mimicking human clinical use, was not associated with fetal malformations, but there was an increase in embryonic loss relative to controls.

Imipenem/cilastatin administered to pregnant cynomolgus monkeys during organogenesis at 40 mg/kg/day by bolus intravenous injection caused significant maternal toxicity including death and embryofetal loss."

Relebactam: Study reports for MK-7655 (relebactam) definitive embryo-fetal studies in mice, rats, and rabbits are reviewed below.

Study title/ number: MK-7655: Subcutaneous Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Mice/ TT #12-7330

Key Study Findings

- MK-7655 was administered subcutaneously to female mice at doses of 0, 80, 200, or 450 mg/kg/day once daily from GD 6 through 17. Subcutaneous dosing resulted in reduced plasma C_{max} and AUC exposure in mice compared to intravenous dosing in rats and rabbits.
- There was no evidence of maternal or developmental toxicity in the MK-7655-treated groups except for an increased litter incidence of skull bone and vertebral malformations in high-dose fetuses and an increased litter incidence of cleft palate and skull bone malformations in low-dose fetuses and high-dose fetuses compared to control values.
- Based on the results of this study, a NOAEL dose for developmental toxicity could not be determined. The LOAEL dose was considered to be the low dose, 80 mg/kg/day, which was associated with plasma C_{max} and AUC values of 297 mcM and 493 mcM•hr respectively and a 1.3-fold exposure margin compared to the maximum recommended human dose for relebactam based on AUC comparison.

Conducting laboratory and location:	Merck Research Laboratories, West Point, Pennsylvania, U.S.A.
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle, Group 1), 80 mg/kg/day (Group 2), 200 mg/kg/day (Group 3), and 450 mg/kg/day (Group 4) administered once per day.
Route of administration:	subcutaneous
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Mouse/ Crl:CD1(ICR)
Number/Sex/Group:	20 females/group
Satellite groups:	Toxicokinetic animals: 4 females in Group 1, 8 females in Groups 2-4.
Study design:	Pregnant females scheduled for cesarean section were dosed from Gestation Day (GD) 6 through 17 before cesarean section on GD 18. Toxicokinetic females were dosed from GD 6

	through GD 13 before euthanasia on GD 13.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	All animals survived until their scheduled termination.
Clinical Signs	No MK-7655-related clinical signs were observed.
Body Weights	MK-7655 administration did not alter maternal body weights.
Necropsy findings Cesarean Section Data	There were no MK-7655-related effects on Cesarean section data. Embryonic/fetal survival as assessed by the numbers of corpora lutea, implantations, and live fetuses per female and the derived peri- and post implantation loss calculations were similar in all groups and unaffected by MK-7655 treatment. Also, live fetal weights were not altered by treatment with MK-7655.
Necropsy findings Offspring	There were no MK-7655-related increases in visceral malformations or variations. No fetal coronal malformations or variations were observed in any group and delayed ossifications were not increased in any group. Individual skeletal malformations and variations were also not increased in a MK-7655 dose-related manner. Only zero or one fetus with each recorded malformation type (skull bone malformation, cervical vertebra malformation, lumbar vertebra malformation, axial skeletal malformation, and absent and extra vertebra) was observed in the MK-7655 HD group or the control group. However, the sum of all the fetuses/litters affected by any skeletal malformation was increased in the MK-7655 treatment groups compared to control values with 1/1, 4/4, 3/1, and 5/4 fetuses/litters corresponding to litter incidence values of 5.3%, 20%, 5.3%, and 21% in the control, LD, MD, and HD groups respectively. The increase in total fetal and litter skeletal malformations did not occur in a clear MK-7655 dose-dependent manner, and all the skeletal malformations in the MD group occurred in only one litter. However, the incidence of total fetal/litter malformations in HD animals (5/4) was substantially increased compared to the control incidence (1/1) suggesting an MK-7655-related effect. Also, the litter incidence of two malformations, externally detected cleft palate (15%) and skull bone malformations (15%) in LD mice exceeded the litter incidence in the Merck historical control database for cleft palate (mean of 5.4%; range of 0 - 11%) and skull bone malformations (mean of 0%; range of 0 – 0%) and was increased compared to the litter incidence of both findings in the control, MD and HD groups (0%, 0%, and 5.3% respectively). Because both cleft palate and skull bone malformations are considered to be rare events, the increased litter incidence of these findings in the LD group compared to concurrent and historical control incidences is considered to be a drug related event.

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: MK-7655: Intravenous Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats/ TT #12-7320

Key Study Findings

- There was no evidence of maternal or developmental toxicity at any MK-7655 dose level.
- The NOAEL for both maternal and developmental toxicity was considered to be the high dose of 450 mg/kg/day which was associated with plasma C_{max} and AUC values of 5440 mcM and 2800 mcM•hr respectively and a 7.2-fold exposure margin compared to the maximum recommended human dose for relebactam based on AUC comparison.

Conducting laboratory and location:	Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, West Point, Pennsylvania, U.S.A.
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (Group 1), 50 mg/kg/day (Group 2), 150 mg/kg/day (Group 3), 450 mg/kg/day (Group 4) administered once per day
Route of administration:	Intravenous via tail vein
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Rat, Sprague-Dawley, Crl:D(SD)
Number/Sex/Group:	Main Study: 20 females/Group
Satellite groups:	Toxicokinetic animals: 4 females in Group 1, and 8 females/group in Groups 2-4.
Study design:	Pregnant females scheduled for Cesarean section were dosed from Gestation Day (GD) 6 through GD 20 before Cesarean section on GD 21. Toxicokinetic females were dosed from GD 6 through GD 15 before euthanasia on GD 15.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No MK-7655 related mortality was observed
Clinical Signs	No MK-7655-related clinical signs were observed
Body Weights	There were no MK-7655-related changes in mean maternal body weight gain or mean body weight gain adjusted for total fetal weight.
Necropsy findings Cesarean Section Data	Embryo-fetal survival in the MK-7655 treatment groups was similar to control values for the numbers of corpora lutea, implantations, live fetuses per female, and the derived pre- and postimplantation loss. In addition, sex ratios and fetal weights were not altered by MK-7655 administration at any dose.
Necropsy findings Offspring	No MK-7655-related increases in external, visceral, coronal, or skeletal malformations or variations were observed. Incomplete ossification of

	fetal bones was not significantly increased in any of the MK-7655 dose groups.

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: MK-7655: Intravenous Embryo-Fetal Developmental Toxicity Study in Rabbits/ TT #15-7200

Key Study Findings

- There were no MK-7655-related deaths, changes in maternal body weight or food consumption, or maternal gross observations at any dose level. The only clinical sign was discolored (orange) urine in all the animals administered MK-7655 with dose-related incidence.
- Fetal external, visceral, and coronal malformations and variations were not increased in any of the MK-7655 treatment groups compared to control values, but the combined fetal/litter incidence of skeletal hyoid bone malformations and variations (hyoid bone anomalies) was increased in the high-dose group compared to concurrent control values. However, the litter incidence of hyoid bone anomalies in the high-dose group (28%) was similar to the upper range of litter incidences for hyoid bone anomalies in comparable historical control databases. Thus, the increase in hyoid bone anomalies was not considered to be clearly drug related.
- The NOAEL for developmental toxicity was considered to be 450 mg/kg/day which was associated with plasma C_{max} and AUC values of 7200 mcM and 9490 mcM•hr respectively and a 24-fold exposure margin compared to the maximum recommended human dose for relebactam based on AUC comparison.

Conducting laboratory and location:	Merck Research Laboratories, West Point, Pennslyvania, USA.
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (Group 1), 35 (Group 2), 275 (Group 3), and 450 (Group 4) mg/kg/day administered once per day.
Route of administration:	Intravenous via the ear vein with an injection rate of 5 ml/min and a dose volume of 10 ml/kg
Formulation/Vehicle:	0.9% sodium chloride in water for injection, USP
Species/Strain:	Rabbit, New Zealand White
Number/Sex/Group:	Females designated for Cesarean section: 19/sex/group.
Satellite groups:	Toxicokinetic animals: 4/sex/group
Study design:	From GD 7 through 20, females received 0 (0.9% Sodium Chloride) 35, 275, or 450 mg/kg/day of MK-7655 once daily intravenously via the ear vein. Toxicokinetic blood samples were obtained

	on GD 15. On GD28, all surviving females were euthanized and uterine contents were examined.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No MK-7655-related deaths occurred.
Clinical Signs	Rabbits treated with MK-7655 exhibited orange discolored urine in a dose-related manner for incidence.
Body Weights	No MK-7655-related changes in maternal body weight were observed.
Necropsy findings Cesarean Section Data	There were no MK-7655-related effects on embryonic/fetal survival. The number of corpora lutea, implantations, and live fetuses per female were similar in all groups as were fetal sex ratios, and fetal weights for male and female offspring. Placenta morphology was normal for most placentas in most groups with 2/158, 0/174, 1/157, 0/170 abnormal placentas observed in the vehicle control, LD, MD, and HD groups.
Necropsy findings Offspring	No MK-7655-related increases in fetal external, visceral, or coronal malformations or variations were observed. Also, the incidence of fetuses and litters with skeletal malformations and variations in the torso, limb area, and head were similar in all groups. However, the total number of hyoid bone malformations and variations was increased in the MK-7655 HD group compared to control values. The fetal/litter incidence of hyoid bone malformations was increased in the HD group (3/3) compared to the control group (1/1) and the LD (35 mg/kg/day; 0/0) and MD (275 mg/kg/day; 0/0) groups. Also, the incidence of fetuses/litters with a variation of the hyoid bone in the LD, MD, and HD groups (2/1, 2/1 and 5/3 respectively), was increased in a MK-7655 dose-related manner compared to control values (1/1). Although 3 of the HD fetuses with a hyoid bone variation occurred in 1 litter, the number of litters with hyoid bone variation in the HD group (3) was still increased compared to the number of control litters (1). Also, the sum of hyoid bone malformations and variations referred to as hyoid bone anomalies (fetal/litter incidences) was increased in the HD group (8/5) compared to the control (2/2), LD (2/1), and MD (2/1) groups. The litter incidence of hyoid bone anomalies (malformations and variations) was 28% in the high-dose group compared to 11% in the control group. However, because the 28% litter incidence of hyoid bone anomalies in the HD group was similar to the highest incidences of this finding in comparable historical control databases (25-29%), the increased incidence was not considered to be clearly drug related.

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Imipenem/Cilastatin: The information on the 2018 PRIMAXIN® product label describing the pre-postnatal effects of imipenem and cilastatin is as follows: "No adverse effects on the fetus or on lactation were observed when imipenem-cilastatin sodium was administered

subcutaneously to rats late in gestation at dosages up to 320 mg/kg/day, 2.1 times the maximum recommended daily human dose (on a mg/m^2 body surface area basis)."

Relebactam: The study report for a MK-7655 (relebactam) pre-postnatal study in rats is reviewed below.

Study title/ number: MK-7655: Intravenous Pre- and Postnatal Developmental Toxicity Study in Rats/ TT #15-7050

Key Study Findings

- There were no MK-7655-related deaths, changes in maternal body weight or food consumption, or maternal gross observations at any dose level.
- There was no evidence of developmental toxicity at any dose level.
- The NOAEL for maternal and embryo-fetal toxicity was considered to be the high dose of 450 mg/kg/day which was associated with plasma C_{max} and AUC values of 5380 mcM and 3020 mcM•hr respectively and a 7.7-fold exposure margin compared to the maximum recommended human dose for relebactam based on AUC comparison.

Conducting laboratory and location:	Merck Research Laboratories, West Point, Pennsylvania.
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (Group 1, vehicle control), 65 (Group 2), 200 (Group 3), and 450 (Group 4) mg/kg/day administered once per day.
Route of administration:	Intravenous via tail vein
Formulation/Vehicle:	0.9% Sodium Chloride in Water for Injection
Species/Strain:	Rat, Sprague-Dawley
Number/Sex/Group:	Main Study (females designated for parturition): 20 females/group
Satellite groups:	Toxicokinetic animals: 4 females/group
Study design:	Pregnant females in the Main Study were dosed from GD 6 through LD 20 before the scheduled euthanasia on LD 21. Pregnant Toxicokinetic females were dosed from GD 6 until GD 15 before toxicokinetic sampling and euthanasia on GD 15. On PND 21, 2 pups/sex/ litter were retained when possible for mating. Remaining pups were euthanized. Mated F1 females were individually housed during the gestation period, and then euthanized between GD 15 and 17. The uterus of each mated female was examined to determine pregnancy status.

If there was no gross evidence of pregnancy, the uterus was stained to visualize implantation sites. Corpora lutea were counted as were uterine implants which were classified as live fetus, dead fetus, or resorption and live fetuses were euthanized.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Generation	Major Findings
F0 Dams	No MK-7655-related maternal deaths, clinical signs or gross pathology were observed. Uterine Content: The mean number of females with live pups and the mean length of gestation were similar in all groups. There were no external malformations or variations or altered sex ratios in F1 pups in any of the MK-7655 groups.
F1 Generation	No MK-7655-related deaths, clinical signs, or changes in body weight were observed during the preweaning or postweaning periods. Physical Development: There were no MK-7655-related effects on the mean day of occurrence for vaginal opening or preputial separation. Neurological Assessment: There were no MK-7655-related effects on passive avoidance, auditory startle habituation, or open-field motor activity. Reproduction: There were no MK-7655-related effects on mating performance and fertility. Also, on GD 15, there were no MK-7655-related effects on embryonic/fetal survival based on similar numbers of corpora lutea, implantations, and live fetuses per pregnant F1 female.
F2 Generation	F2 generation offspring were not assessed except for fetal survival on GD 15 (as noted above) which was not changed in any of the MK-7655 groups compared to control values.

5.5.5 Other Toxicology Studies

MK-7655: Subcutaneous and Intravenous Toxicity and Toxicokinetic Study in Juvenile Rats. (Study No.: TT #16-7090)

Methods: In this GLP-compliant study, juvenile rats were administered vehicle or 65, 200, and 450 mg/kg/day MK-7655 once daily by bolus SC injection from postnatal day (PND) 14 to PND 34 and by IV injection via tail vein over a period of two minutes per animal through PND 56 or 57. Each dose group consisted of 3 (control) or 5 (test article-treated) litters with 4 fostered pups/sex/litter. Each dose group litter was composed of pups from different litters and had no

littermates of the same sex. All pups in a given litter received the same dose level or vehicle only. The rats were weaned on PND 21. Twelve animals/sex/group were necropsied on PND 56 or 57 (Main Study necropsy) at the end of the dosing period in postnatal week (PNW) 8, and eight animals/sex in the control and 450 mg/kg/day groups were necropsied on PND 85 (PNW 12) (Recovery necropsy) following a 4-week treatment-free period.
Results: There was no evidence of MK-7655-related toxicity based on clinical signs, body weight, food consumption, gross pathology findings, organ weights, histopathology findings, femur length and developmental landmarks. The no-observed-effect level was considered to be the high dose of 450 mg/kg/day. Toxicokinetic Parameters for plasma MK-7655 from PND 56/57 samples are shown in the table below.

Table 3: Mean (± SE) Plasma MK-7655 Toxicokinetic Parameters in Juvenile Rats Following Dosing of MK-7655: Postnatal Day 56/57. (Table from the Study Report)

Dose (mg/kg/day)[a]	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
65	Female	286 ± 19.2	536 ± 15.6	0.050 ± NC
	Male	298 ± 10.9	532 ± 28.7	0.050 ± NC
	All	292 ± 9.30	534 ± 15.1	0.050 ± NC
200	Female	970 ± 42.5	1930 ± 88.9	0.050 ± NC
	Male	995 ± 28.2	1870 ± 19.1	0.050 ± NC
	All	983 ± 24.6	1900 ± 43.7	0.050 ± NC
450	Female	2240 ± 187	3990 ± 188	0.050 ± NC
	Male	2470 ± 98.7	3840 ± 419	0.050 ± NC
	All	2350 ± 106	3920 ± 215	0.050 ± NC

NC = Not Calculated

[a]MK-7655 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.0861 µM) of the bioanalytical method.

Study Title: Bovine Corneal Opacity and Permeability Test (BCOP). (Study No.: TT #13-7802)
Methods: This GLP-compliant study was conducted in 2013 (b) (4) (b) (4) Isolated bovine eyes immersed in Hanks Balanced Salt Solution in a refrigerated container were obtained on the experimental start date. Seven intact, unblemished corneas were dissected free from the eyes were mounted in holders that were separated into anterior and posterior chambers that were filled separately were Minimal Essential Medium MEM, and before the corneas were allowed to equilibrate for 1-2 hours at 32°C. Before dosing, a pre-exposure determination of opacity was made for each control cornea (2 corneas) and MK-7655-test cornea (5 corneas). Subsequently the anterior chambers were filled with MEM (control corneas) or 0.75 ml of a 20% suspension of L-002118412-002D021 (MK-5675, lot No.: L-002119412-002D021). After 4 hours of exposure, opacity measurements were conducted for the control and treated corneas. Subsequently corneas were incubated with 1 ml of 0.5% sodium fluorescein dye solution in the anterior chamber for 90 minutes followed by permeability measurements based on spectrophotometric measurement of the optical density at 490 nm in the posterior chamber which was directly related to the amount of dye that

passed through the cornea. Opacity and permeability (optical density) scores were calculated for each cornea according to predetermined scales and a combined In Vitro score was calculated
Results: The mean optical density scores for the control and treated corneas were 0.025 and 0.057 respectively. The opacity score for control and treated corneas averaged 0 and -0.06 respectively. The calculated mean In Vitro score for the treated corneas was -0.12 which is consistent with a non-irritant classification[1].

[1] Southee JA, 1998: Evaluation of the Prevalidation Process, Part 2, final report, Volume 2, The Bovine Corneal Opacity and Permeability (BCOP) Assay. European Community Contract No.: 11279-95-10F IED ISP GB.

Study Title: Acute Dermal Irritation/Corrosion in Rabbits. (Study No.: TT # 13-7803)
Methods: This GLP-compliant study was conducted (b) (4) (b) (4) in 2013. Healthy New Zealand White rabbits (2 males - 1 female) received a single dermal (topical) dose of 500 mg L-002118412-002D021 (MK-7655, lot No.: L-002119412-002D021) at a single site which was subsequently wrapped with semi-occlusive dressing. After 4 hours, the wrappings were removed, and erythema and edema were scored at 1, 24, 48 and 72 hours following patch removal. Skin at the exposure site was also evaluated for ulceration and necrosis or any evidence of tissue destruction at the same timepoints. Based on the mean scores for erythema/eschar and edema, a Modified Primary Irritation Index was calculated.
Results: Erythema and edema at the dermal exposure site was absent in all three rabbits at each observation timepoint. The Modified Primary Irritation Index was 0.

Study Title: Local Lymph Node Assay in Mice (LLNA). (Study No.: TT #13-7804)
Methods: This GLP-compliant study was conducted (b) (4) (b) (4) in 2013. Five groups of healthy female CBA/J mice (5 mice/group) were topically treated with vehicle (DMSO), the positive control agent (25% hexylcinnamaldehyde in DMSO) or 5%, 10% and 25% MK-7655 dissolved in DMSO. Solutions were applied topically to the dorsum of each ear once daily for three consecutive days. Ear thickness measurements were used as a measurement of skin irritation, and measurements were performed on Days 1 and 3 before dosing, and on Day 6 before animal euthanasia. Subsequently mice were administered an intraperitoneal injection of the thymidine analog, 5-bromo-2'-deoxy-uridine (BrdU) five days after the initial dose and 5 hours prior to euthanasia. Following euthanasia, the auricular lymph nodes were isolated from each mouse and single-cell suspensions of lymph node cells (LNC) were generated. The LNC suspensions were analyzed by flow cytometry for BrdU incorporation and the total number of LNC. The number of proliferating LNC stained with BrdU was considered to be a measure of the proliferative response of the local lymph node. The stimulation index (SI) was calculated by dividing the proliferative response of each MK-7655-treated or positive control-treated animal by the mean proliferative response of the vehicle control group. Test article groups that yielded a stimulation index ≥ 3 were characterized as sensitizing substances.

Results: None of the tested MK-7655 concentrations resulted in increased ear thicknesses compared to vehicle control values on either Day 3 or 6. In contrast, On Day 6, the positive control agent, 25% HCA, produced a 35% increase in ear thickness compared to pretest values and a 133% greater increase in ear thickness compared to the increase in ear thickness experienced by vehicle control animals.

6 Clinical Pharmacology

6.1 Executive Summary

The Office of Clinical Pharmacology reviewed the information contained in NDA 212819. The clinical pharmacology information submitted in the application supports the approval of RECARBRIO (imipenem/cilastatin/relebactam; herein referred to as IMI/REL) for injection (for intravenous use) for the treatment of cUTI and cIAI in patients 18 years of age and older with limited or no alternative therapies available. See Table 7 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 7. Summary of OCP Recommendations and Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The evidence of effectiveness of IMI/REL in patients with cUTI and cIAI was provided in part by the Agency's previous finding of safety and effectiveness of imipenem, nonclinical PK/PD analyses and probability of target attainment (PTA) simulations using clinical PK data.
General dosing instructions	The recommended dosing regimen is 500 mg imipenem, 500 mg cilastatin, 250 mg relebactam by intravenous (IV) infusion over 30 minutes every 6 hours in patients 18 years of age and older with creatinine clearance (CLCr) 90 mL/min or greater.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose reductions are recommended in patients with renal impairment (See Section 6.2.2).
Labeling	Recommendations were communicated to the Applicant.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Table 8 provides a summary of the clinical pharmacology characteristics of IMI/REL.

Cilastatin (CIL) does not possess antibacterial activity and is coadministered to prevent metabolism of IMI by renal dehydropeptidase. Thus, any clinically meaningful change in CIL PK would also manifest as a clinically meaningful change in IMI PK.

In Study PN001, it was demonstrated that there is no clinically relevant DDI between REL and CIL. Therefore, co-administering IMI and REL as a fixed drug combination (FDC) is expected to have no effect on the PK of CIL. Considering this rationale, the evaluation of CIL PK through a population PK (popPK) model was not pursued in this review.

Table 8. Clinical Pharmacology Characteristics of Imipenem/Relebactam

Distribution	The binding of REL to human plasma proteins is approximately 22% and is independent of concentration at a range of 5 and 50 µM. The binding of IMI to human plasma proteins is approximately 20%. The median steady state volume of distribution of REL and IMI is 19 L and 24.3 L, respectively [a].
Elimination	The mean terminal half-life of REL and IMI is approximately 1.2 hours and 1.0 hour, respectively [a].
	Metabolism REL is not significantly metabolized (<10% of the dose). Post-excretory metabolism of IMI is mediated by renal dehydropeptidase, which is inhibited by CIL.
	Excretion Both IMI and REL are primarily excreted by the kidneys through glomerular filtration and active tubular secretion. The % of unchanged drug excreted in urine (fe) is 63% for IMI and >90% for REL [b].

[a] Volume of Distribution and $t_{1/2}$ for IMI and REL are taken from popPK analyses
[b] Following administration of 500 mg IMI co-administered with 250 mg REL to healthy subjects every 6 hours daily for 7 days

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosage regimen of RECARBRIO is 1.25 grams (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) administered by IV infusion over 30 minutes every 6 hours in patients 18 years of age and older with creatinine clearance (CLCr) 90 mL/min or greater. The total duration of treatment is 4 to 14 days.

Therapeutic Individualization

No clinically significant differences in the pharmacokinetics of IMI, CIL, or REL were observed based on age, gender, or race/ethnicity. The effect of hepatic impairment has not been studied; however, REL, as well as CIL are almost entirely excreted unchanged in urine and no clinically relevant metabolism occurs. IMI is partly metabolized in the kidney by dehydropeptidases. Thus, hepatic impairment is not expected to have an effect on the PK of IMI or REL.

However, both IMI and REL exposure in plasma increased with decreasing renal function in a dedicated renal impairment study (Study P005). The fraction of dose excreted unchanged in urine (fe) also decreased progressively from mild to severe renal impairment and was lower in subjects with renal impairment as compared to subjects with normal renal function for both IMI and REL. Further, the effect of renal impairment, as measured by CLCr, on REL and IMI PK was identified as a significant covariate in popPK analysis using pooled clinical data. Thus, we recommend the dosage of IMI/REL in patients with renal impairment be adjusted as presented in Table 9. We also recommend IMI/REL be administered following dialysis for patients maintained on hemodialysis because both IMI and REL are substantially eliminated by hemodialysis.

Patients with Renal Impairment
REL is primarily eliminated (~90%) by renal excretion. As expected for a drug primarily eliminated by the kidneys, REL exposures increase with decreasing renal function. The exposure increase is clinically meaningful, so dose reduction in patients with renal impairment is recommended (Table 9).

Table 9. Dosage of IMI/REL According to Renal Function

Creatinine Clearance (mL/min) [1]	**IMI/REL** [2]
≥90	500/250 mg every 6 hours
89 to 60	400/200 every 6 hours
30 to 59	300/150 every 6 hours
15 to 29	200/100 mg every 6 hours
ESRD on hemodialysis	200/100 mg every 6 hours [3]

[1] As calculated using the Cockroft-Gault formula
[2] Infused over 30 minutes
[3] Administration should be timed following hemodialysis

Outstanding Issues

None.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

<table>
<tr><th colspan="2">Pharmacology</th></tr>
<tr><td>Mechanism of Action</td><td>IMI is a bactericidal carbapenem antibacterial that inhibits cell wall synthesis by inhibition of penicillin binding proteins (PBPs). CIL is a renal dehydropeptidase-I inhibitor that limits the renal metabolism of imipenem and does not have antibacterial activity.

REL is a diazabicyclooctane (DABCO) beta-lactamase inhibitor of some Ambler class A and C beta-lactamases. Relebactam has no intrinsic antibacterial activity.</td></tr>
<tr><td>Active Moieties</td><td>Imipenem (IMI) and Relebactam (REL)</td></tr>
<tr><td>QT Prolongation</td><td>At a single intravenous dose of 1150 mg (4.6 times the recommended dose), REL does not prolong the QT interval to any clinically relevant extent (Study MK7655-009).

Imipenem is not known to cause QT prolongation clinically.</td></tr>
<tr><th colspan="2">General Information</th></tr>
<tr><td>Bioanalysis</td><td>Multiple validated HPLC-MS/MS assays were used to determine concentrations of REL, CIL and IMI in human plasma, human urine, human dialysate, mouse blood, and the extracapillary space of hollow fiber cartridges in hollow fiber infection (HFIM) experiments. All bioanalytical assays met the requirements for specificity, sensitivity, accuracy, and precision.</td></tr>
<tr><td>Healthy vs. Patients</td><td>Overall, the effect of active bacterial infection on IMI PK is not expected to be clinically meaningful considering the modest effect on exposures still results in >90% PTA in patients with active bacterial infection in all renal function categories.</td></tr>
<tr><td>Drug Exposure at steady state following the therapeutic dosing regimen</td><td>The steady state PK of IMI/REL following 7-day administration of 500 mg IMI + 250 mg REL to healthy subjects is shown below:

<table>
<tr><td></td><td>IMI</td><td>REL</td></tr>
<tr><td></td><td colspan="2">Mean ± SD</td></tr>
<tr><td>$AUC_{0\text{-}6hr}$ (μM*hr)</td><td>140 ± 23.1</td><td>82.7 ± 13.8</td></tr>
<tr><td>C_{max} (μM)</td><td>109 ± 25.9</td><td>49.4 ± 11.0</td></tr>
</table>
$AUC_{0\text{-}6hr}$=area under the concentration time curve from 0 to 6 hours; C_{max}=Concentration at end of infusion</td></tr>
</table>

<table>
<tr><td></td><td>The popPK model based steady-state Geometric Mean (% Geometric Co-efficient of Variation) plasma PK of IMI/REL following multiple IV infusions of 500 mg IMI + 250 mg REL /every 6 Hours in patients with CLcr 90 mL/min or greater is shown below:

<table>
<tr><td></td><td>IMI</td><td>REL</td></tr>
<tr><td></td><td colspan="2">Mean ± SD</td></tr>
<tr><td>AUC_{0-24hr} (μM*hr)</td><td>573.9 ± 321.2</td><td>427.3 ± 190.3</td></tr>
<tr><td>C_{max} (μM)</td><td>104.3 ± (61.4)</td><td>64.0 ± (27.3)</td></tr>
</table>
AUC_{0-24hr}=area under the concentration time curve from 0 to 24 hours; C_{max}=Concentration at end of infusion</td></tr>
<tr><td>Range of effective dose or exposure</td><td>The determination of efficacy of IMI/REL relies in part on the FDA's previous findings of the effectiveness of imipenem in the treatment of cUTI and cIAI, in vitro and animal data demonstrating that REL restores activity of IMI against IMI-nonsusceptible gram-negative organisms expressing some Class A and some Class C β-lactamases, and by the probability of target attainment (PTA) analyses for REL conducted by the FDA.</td></tr>
<tr><td>Maximally tolerated dose (MTD) or exposure</td><td>Subjects tolerated REL as single doses up to 1150 mg, multiple doses up to 625 mg every 6 hours for 7 days, or multiple doses up to 500 mg every 6 hours for 14 days (Study P001V01MK7655). Higher doses were not evaluated.</td></tr>
<tr><td>Dose proportionality</td><td>REL $AUC_{0-\infty}$ and C_{max} increased in an approximately dose-proportional manner following single doses of REL ranging from 25 mg to 1150 mg. REL AUC_{0-6hr} and C_{max} also increased in an approximately dose proportional manner when 50 to 625 mg REL were coadministered with 500 mg IMI q6h for 7 days (Study P001V01MK7655).</td></tr>
<tr><td>Accumulation</td><td>The accumulation ratio for the dosing regimen of 250 mg REL coadministered with 500 mg IMI q6h x 7 days was approximately 1.0 for both REL and IMI (Study P001V01MK7655).</td></tr>
<tr><td>Variability</td><td>The between-subject variability (BSV) of REL clearance (CL) and volume of distribution (VD), as estimated in a population pharmacokinetic analysis of patients and healthy subjects, were 45% and 60%, respectively. The between subject variability (BSV) of IMI CL and VD were 52% and 74%, respectively.</td></tr>
<tr><td>Volume of Distribution</td><td>The mean steady state volume of distribution of REL is 19.0 L.</td></tr>
</table>

Plasma Protein Binding	The binding of REL to human plasma proteins is approximately 22% and is independent of concentration at a range of 5 to 50 µM. The binding of IMI to human plasma proteins is approximately 20%.
Substrate of transporter systems	In vitro, REL is a substrate of renal transporters, OAT3 and OAT4, and multidrug and toxin extrusion protein 1 and 2K (MATE1 and MATE2K). However, the contribution of active renal secretion to the renal clearance of REL was <30% (see Section 18.4.1) and, thus, the maximum increase in AUC of REL by the transporter inhibitors would be <1.5 fold, which is not considered to be clinically meaningful (Studies PK004MK7655, PK006MK7655, PK009MK7655, PK012MK7655). A clinical DDI trial demonstrated that REL exposure was not meaningfully increased (24% increase in AUC) when co-administered with probenecid (Study PN019).
Half-life	The mean terminal half-life of REL is approximately 1.2 hours. The mean terminal half-life of IMI is approximately 1.0 hour.
Metabolism	
Fraction metabolized (% dose)	REL is not significantly metabolized (<10% of the dose). Post-excretory metabolism of IMI is mediated by renal dehydropeptidase, which is inhibited by CIL.
Excretion	
Primary excretion pathways	The major route of elimination for both IMI and REL is glomerular filtration and active tubular secretion. Active tubular secretion accounts for approximately 30% of the total body clearance of REL. Following administration of 500 mg IMI co-administered with 250 mg REL to healthy subjects every 6 hours daily for 7 days, 63% of IMI and >90% REL is excreted unchanged in urine (Study PN001).
Drug-drug Interactions	
Inhibition/Induction of metabolism	Results from *in vitro* studies suggest REL does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 at clinically relevant concentrations (Study PK002MK7655). Results from *in vitro* studies suggest REL does not induce CYP1A2, 2B6, or 3A4 at clinically relevant concentrations (Studies PK002MK7655, PK007MK7655).
Inhibition/Induction of transporter systems	REL was not an inhibitor of the following transporters at clinically relevant concentrations: P-gp, OATP1B1-, OATP1B3-, OAT1-, OAT3-, OCT2, MATE1-, MATE2K-, BCRP-, and BSEP (Studies PK006MK7655, PK008MK7655, PK009MK7655).
Interaction between components of the fixed dose combination	There are no interactions among the individual components in the fixed dose combination (FDC) (Study P001V01MK7655).

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The evidence of effectiveness of IMI/REL for the treatment of adult patients with cUTI or cIAI is reliant in part on the Agency's previous finding of the safety and effectiveness of IMI, *in vitro* and animal data demonstrating that REL restores activity of IMI against IMI-nonsusceptible Gram-negative organisms expressing some Class A and some Class C β-lactamases, and PTA analyses for REL conducted by the FDA.

Both IMI and REL PK/PD targets were derived using IMI MICs in the presence of a fixed concentration of 4 μg/mL REL. The average concentration (C_{avg}) of REL administered at 250 mg every 6 hours in healthy volunteers was 3.75 μg/mL. The mean unbound (free) C_{avg} in patients as predicted by popPK modeling was 4.4 μg/mL. The 4 μg/mL concentration is presumed to correlate with beta-lactamase expression and distinguish between IMI/REL susceptible Gram-negative isolates which express beta-lactamases susceptible to inhibition by REL versus isolates expressing enzymes not susceptible to inhibition.

The rationale to use the beta-lactam (BL) MIC for the PK/PD index of the beta-lactamase inhibitor (BLI) has been discussed in previous reviews of BL/BLI combination products. Briefly, the rationale assumes that the expression levels of the beta-lactamase is correlated with the MIC of the BL at BLI concentrations that are presumed to be sufficient to restore the bactericidal activity of the BL in bacteria expressing a high level of beta-lactamase enzymes. The BLI exposure (e.g., AUC) required to restore bactericidal activity of BL (i.e., BLI exposure required to inhibit beta-lactamase) in beta-lactamase-expressing isolates is dependent on the expression level of beta-lactamase (i.e., BL MIC in the presence of BLI). Thus, the BLI PK/PD index is often expressed as a combination of BLI exposure and BL MIC (e.g., AUC/MIC).

The Applicant used a REL bacteriostatic PK/PD target (i.e., AUC/MIC of REL required to restore IMI activity to net-stasis of CFU from baseline for beta-lactamase-expressing (IMI-resistant) isolates) derived from neutropenic mouse thigh infection model data ($fAUC_{0\text{-}24hr}$/MIC = 5.2). The Applicant used an IMI PK/PD target for 2-log reduction of CFU from baseline of 6.5% fT>MIC (i.e., % time to dosing interval for free drug concentration to exceed MIC), where MIC is changed as a function of REL concentration (see Section 19.4 for details), derived from hollow fiber infection models (HFIM) to assess probability of joint PK/PD target attainment. Based on the Applicant's analysis, the probability of IMI and REL joint target attainment was greater than 90% for *P. aeruginosa* and Enterobacteriaceae with an IMI/REL MIC ≤4 μg/mL. However, the Clinical Pharmacology review team concluded that the IMI PK/PD target is not acceptable as it is based on uninterpretable HFIM data. Instead, the review team decided that the PTA analysis for IMI is not needed and evaluation of the PTA for REL alone is sufficient to support the effectiveness of IMI/REL because of the following reasons: (a) there is no PK interaction between IMI and REL, (b) thus, antibacterial activity (i.e., PK/PD) of IMI against beta-lactamase-expressing pathogens would be considered identical to that against IMI susceptible (i.e., non-

beta-lactamase-expressing) pathogens as long as REL completely inhibits the beta-lactamase enzymes, (c) the PK/PD target of IMI alone has already been established and the approved doses are sufficient to attain the PK/PD target, (d) the proposed IMI dose in IMI/REL is the same as the approved IMI alone dose, (e) the proposed susceptibility breakpoints for IMI/REL are numerically the same as those for IMI alone, and (f) REL has no intrinsic antibacterial activity.

The Clinical Pharmacology review team conducted an independent PTA analysis for REL. We determined the REL AUC/MIC targets using pooled data from all mouse thigh infection experiments (see Section 15.4.2). The REL AUC/MIC targets in these experiments varied with the IMI dose (e.g., high REL target for low doses of IMI). The REL 1-log kill AUC/MIC targets (i.e., AUC/MIC of REL required to restore IMI activity to 1-log reduction of CFU from baseline for beta-lactamase-expressing isolates) from our analysis were 7.5 and 14.4 for the mean and 97.5th percentile, respectively. Based on the proposed IMI/REL susceptibility breakpoint of 2 µg/mL, the corresponding REL AUC targets were 15 and 28.8 µg·h/mL for AUC/MIC of 7.5 and 14.4, respectively. The REL population PK model was used to simulate REL $AUC_{0\text{-}24hr}$ at the recommended doses. At the IMI/REL susceptibility breakpoint of 2 µg/mL, our analysis demonstrates that the probabilities of REL target attainment for the 97.5th percentile of AUC/MIC target (i.e., 14.4) would be 100% regardless of renal function (see Section 15.4.2).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's proposed dosing regimen is supported by the results of our PK/PD target attainment analyses as discussed above.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No clinically significant differences in the pharmacokinetics of IMI, CIL, or REL were observed based on age, gender, or race/ethnicity. Hepatic impairment is also not expected to have an effect on the PK of IMI or REL. However, both IMI and REL exposure in plasma increase with decreasing renal function. Thus, we recommend dosage of IMI/REL in patients with renal impairment be adjusted as presented in Table 9**.** We also recommend IMI/REL be administered following dialysis for patients maintained on hemodialysis.

Renal Impairment
The results of the dedicated renal impairment study (Study P005) showed that the AUCs of REL and IMI increased with the degree of renal impairment. However, the effect of renal impairment on REL PK was larger than that on IMI PK due to a higher fe of REL compared to IMI (see Section 15.4.3). Following a 125 mg dose of REL co-infused with 250 mg IMI, geometric mean $AUC_{0\text{-}\infty}$ increased approximately 1.63-fold, 2.19-fold, and 4.87-fold for REL and by approximately 1.41-fold, 1.53-fold, and 2.51-fold for IMI in subjects with mild (eGFR >50 to <80 mL/min/1.73m^2), moderate (eGFR >30 to <50 mL/min/1.73m^2), and severe (eGFR <30 mL/min/1.73m^2) renal impairment, respectively, compared to age-, gender-, and BMI-matched

subjects with normal renal function. IMI/REL appeared to be well tolerated in Study P005. However, this study only included a single 125 mg IV dose of REL administered to a limited number of subjects (n=6 per group).

The Applicant's proposed dose adjustments of IMI/REL for patients with renal impairment are the same as those recommended in the Primaxin (IMI) label, with REL following the same dose reduction ratio as IMI/CIL. REL is almost exclusively excreted by the kidneys. IMI is also mainly excreted by the kidneys, but to a somewhat lower extent (53-71%). Because the effect of renal impairment on REL is greater, the proposed dose adjustments result in a higher REL exposure in patients with renal impairment than that in patients with normal renal function. However, this higher REL exposure may not be clinically significant. Safety data from P005 demonstrated that a single 125 mg IV dose of REL is generally well tolerated in subjects, regardless of degree of renal impairment. Doses of IMI and REL were adjusted in Studies PN003, PN004 and PN013 for subjects with renal impairment. There were no clinically meaningful differences in the incidence and profile of AEs between subjects with normal renal function and subjects with mild or moderate renal impairment in Studies PN003 and PN004. The relatively small number of subjects with severe renal impairment (0 to 1 subject per treatment group) precluded meaningful conclusions about the impact of more severe renal impairment on the tolerability of IMI + REL in this subgroup. AEs were not summarized by renal function category for PN013 due the smaller sample size. In addition, the predicted AUC and Cmax of REL in patients with renal impairment receiving the reduced dosage are lower compared to the 90th percentile of AUC and Cmax for REL dose of 625 mg every 6 hours in subjects with normal renal function, where no safety findings were observed. The results of this analysis also support that the REL exposure in patients with renal impairment receiving the proposed dosage adjustment would be acceptable in terms of safety.

As expected from higher REL exposure in patients with renal impairment than that in patients with normal renal function, a PTA of >90% is maintained in patients with renal impairment receiving the proposed dose adjustments (See Section 15.4.4).

Collectively, the Applicant's proposed dose adjustments for patients with renal impairment following the current IMI/CIL labeling are acceptable (See Section 6.2.2).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

REL has a low drug-drug interaction (DDI) risk either as a victim or a perpetrator. Evaluation of the effect of inhibition of organic anion transporters (OATs) by probenecid demonstrate d no clinically relevant effect on IMI and REL PK. There are no DDIs among the individual components in the FDC (See Section 6.3.1).

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Three trials were submitted in the NDA (Table 10). PN003 and PN004 were dose ranging, active-controlled trials in the treatment of cUTI and cIAI, respectively. The trials compared two doses of relebactam (125 mg and 250 mg, given concomitantly with 500 mg IMI) with IMI plus placebo. Neither trial was designed to demonstrate the added benefit of REL to the combination of IMI/REL as most of the baseline pathogens in the trials were susceptible to imipenem.

Trial PN013 was a double-blind, comparator-controlled trial in the treatment of infections caused by imipenem-nonsusceptible gram-negative pathogens, including HABP/VABP, cIAI, and cUTI. In this trial IMI/REL was compared with the combination of imipenem and colistimethate sodium.

Table 10. Listing of Clinical Trials Reviewed in Imipenem/Relebactam NDA

Trial	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients randomized	Study Population	No. of Centers and Countries
PN003	Multicenter, double-blind randomized, active-controlled, dose ranging, trial in patients with cUTI	IMI/REL (250 mg) q 6 hours IMI/REL (125 mg) q 6 hours IMI/placebo q 6 hours Imipenem dose 500 mg in all 3 arms Intravenous (IV) or IV+oral. Switch from IV treatment to oral ciprofloxacin permitted following the minimum duration of 4 days of IV treatment	Microbiological response and clinical response at the discontinuation of IV treatment (DCIV) visit, early follow-up visit (EFU, 5 to 9 days post-antibiotic therapy), and late follow-up visit (LFU, 28-42 days post-antibiotic therapy)	4 to14 days/ 28-42 days post-antibiotic therapy	Randomized 250mg:101 125mg:101 Placebo:100	Adult patients with a cUTI or acute pyelonephritis judged by the investigator to be serious (requiring hospitalization and treatment with IV antibacterial therapy)	35 centers and 11 countries enrolled subjects
PN004	Multicenter, double-blind, randomized, active-controlled, dose ranging, trial in patients with cIAI	IMI/REL (250 mg) q 6 hours IV IMI/REL (125 mg) q 6 hours IV IMI/Placebo q 6 hours IV Imipenem dose 500 mg in all 3 arms	Clinical response at the DCIV, EFU, and LFU Visits	4 to 14 days (IV only; no oral switch allowed)/ 28-42 days after IV therapy	250mg: 118 125mg: 116 Placebo: 117	Subjects with cIAI that required hospitalization and treatment with IV antibacterial therapy	46 centers and 20 countries enrolled subjects
PN013	Multicenter, double-blind, randomized, active-controlled trial in adults with imipenem non-susceptible bacterial infections, including HABP/VABP, cIAI, and cUTI (with an additional non-randomized, open-label group)	IMI/REL q 6 hours+ (placebo for CMS q 12 hours) IV IMI q 6 hours+CMS q 12 hours IV IMI/REL (non-randomized) q 6 hours IV Relebactam dose: 250 mg Imipenem Dose: 500 mg	Favorable overall response based on survival (HABP/VABP), composite clinical and microbiological response (cUTI) and clinical response only (cIAI)	5 (cUTI/cIAI) or 7 (HABP/ VABP) to 21 days/ 28 days	Enrolled: IMI/REL:31 IMI+CMS:16 IMI/REL (open label): 3	Adults patients who required hospitalization and treatment with IV antibacterial therapy for a new, persistent, or progressing HABP/VABP, cIAI, cUTI	16 centers and 11 countries enrolled subjects

IMI: imipenem/cilastatin; REL: relebactam (MK-7655); IMI/REL: fixed-dose combination of imipenem/cilastatin/relebactam; CMS: colistimethate sodium (total maximum daily maintenance dose: 300 mg colistin base activity. Loading dose followed after 12 hours by maintenance dose every 12 hours); HABP/VABP: hospital-acquired/ventilator-associated pneumonia.

7.2 Review Strategy

Data Sources

This NDA was submitted in eCTD format. Data sources include study protocols, reporting and statistical analysis plans, clinical study reports, integrated summaries of efficacy and safety, and data sets (in both Study Data Tabulation Module (SDTM) and Analysis Data Model (ADaM) formats). Data sets and software code are available at \\Cdsesub1\evsprod\NDA212819\0000\m5\datasets.

Data and Analysis Quality

Overall, the quality of datasets and analysis was adequate. It was possible to reproduce the primary analyses from the original data source. Blinding/un-blinding procedures were generally well documented. Quality control/assurance procedures were documented. Statistical analysis plans were finalized before unblinding. The quality of the eCTD submission was also adequate. Documents and datasets were generally located in the appropriate place and submitted in the proper format. However, for the cUTI and cIAI trials, PN003 and PN004, protocol deviations/violations were only briefly described in the study reports without submission of electronic data sets.

7.3 Review of Relevant Individual Trials

7.3.1 Study PN003 (cUTI)

Trial Objectives

The primary objective of this trial was to evaluate the safety, tolerability, and efficacy of REL (at 2 doses) plus IMI versus IMI alone with respect to the microbiological response in the treatment of cUTI, including acute pyelonephritis, in adult patients, at completion of IV study therapy (or discontinuation of IV study therapy [DCIV]).

Secondary objectives included:

To evaluate the efficacy of 2 doses of REL (250 mg and 125 mg) plus IMI with respect to

1. the microbiologic response in the treatment of adult patients with imipenem-resistant Gram-negative cUTI at the DCIV visit.

2. the microbiological response in the treatment of adult patients with cUTI as compared to IMI alone at the 5- to 9-day post-antibiotic therapy (early follow-up [EFU]) visit.

3. the clinical response in the treatment of patients with cUTI as compared to the IMI alone group at the DCIV visit.

4. the clinical response in the treatment of patients with cUTI as compared to the IMI alone group at the EFU visit.

5. the proportion of patients with sustained microbiological response and sustained clinical response in the treatment of patients with cUTI as compared to the IMI alone group, measured at the 28- to 42-day post-antibiotic therapy (late follow-up [LFU]) visit.

Trial Design and Endpoints

PN003 was a multi-center, randomized, double-blind, parallel-group, dose ranging, active-controlled trial. Eligible subjects were randomized 1:1:1 to the following groups:

1. REL 250 mg plus IMI 500 mg every 6 hours (q6h)
2. REL 125 mg plus IMI 500 mg q6h
3. Placebo (normal saline) plus IMI 500 mg q6h

The dose or frequency of IV study therapy was adjusted for subjects with renal insufficiency and/or for subjects who weighed <70 kg.

Body Weight (kg)	Creatinine Clearance (mL/min/1.73 m^2)					
	≥71			50-70		
	Imipenem/Cilastatin	MK-7655		Imipenem/Cilastatin	MK-7655	
	All Treatment Groups: Imipenem/Cilastatin	Group 1: MK-7655 (250 mg)	Group 2: MK-7655 (125 mg)	All Treatment Groups: Imipenem/Cilastatin	Group 1: MK-7655 (250 mg)	Group 2: MK-7655 (125 mg)
≥70	500 mg q6h	250 mg q6h	125 mg q6h	500 mg q8h	250 mg q8h	125 mg q8h
60	500 mg q8h	250 mg q8h	125 mg q8h	250 mg q6h	125 mg q6h	62.5 mg q6h
50	250 mg q6h	125 mg q6h	62.5 mg q6h	250 mg q6h	125 mg q6h	62.5 mg q6h
40	250 mg q6h	125 mg q6h	62.5 mg q6h	250 mg q8h	125 mg q8h	62.5 mg q8h
30	250 mg q8h	125 mg q8h	62.5 mg q8h	125 mg q6h	62.5 mg q6h	31.25 mg q6h

† Subjects in Treatment **Group 3** will be administered placebo in a separate infusion bag at the same time as the imipenem/cilastatin infusion. Therefore, the dosing intervals (i.e., q6h, q8h) for placebo also will be adjusted as described for imipenem/cilastatin.

Source: Table 3-2 of study report. MK-7655: REL

Oral ciprofloxacin could be used following the minimum duration (96 hours) of IV study therapy in subjects with adequate response to therapy at the discretion of the investigator. Adequate response was defined as clinical improvement in pre-study symptoms, fever resolved for at least 24 hours, and at least one follow-up urine culture had shown eradication (defined as a uropathogen colony count of $<10^4$ colony forming units [CFU]/mL).

The total duration of antibacterial therapy (IV and subsequent oral ciprofloxacin) did not exceed 14 days. If therapy was needed for longer, IV study therapy was discontinued, and other non-study medication could be administered.

There was an option to switch to the 250-mg REL dose in the study. If after at least 72 hours (up to an additional 48 hours) of initial IV study therapy, the identified pathogen(s) was/were resistant to IMI but may be susceptible to IMI/REL, and the subject did not achieve a favorable clinical response to IV study therapy, the subject could be switched to 250-mg REL (or remain on 250-mg REL for subjects assigned to this group) if requested by the investigator. These subjects would be considered to have unfavorable clinical and microbiological responses at all subsequent visits.

This study was double-blind, except for an unblinded study pharmacist (or qualified designee) at each study center who was not involved in any management or evaluation of safety and efficacy of the subject.

Subjects were evaluated daily for safety and tolerability while on IV therapy. Microbiological response, clinical response, and safety were evaluated at the DCIV, EFU (5-9 days post therapy) and LFU (28 to 42 days post therapy) visits.

For IV test drugs that are followed by a different oral therapy, the cUTI guidance recommends an early assessment (end of IV therapy), prior to the use of the oral therapy, along with the assessment at EFU. This allows for the assessment of the effect of the IV test drug alone and the effect of the IV to oral regimen. The DCIV visit and EFU visit closely match these recommended time points. However, the timings of the visits were based on the duration of IV treatment or total treatment, which can be associated with the effect of treatment and could result in systematic differences across treatments in the timing of these visits. An assessment of the timing of the visits is provided in the results section.

The Applicant's primary efficacy endpoint was microbiological response at the DCIV visit. It was assessed as favorable (eradication) or unfavorable (persistence or persistence with acquisition of resistance) for each subject. This was assessed separately for each pathogen identified at admission. For a favorable overall microbiological assessment, all bacterial uropathogens identified at baseline needed to be "eradicated" in the urine culture collected at the DCIV visit (and must not have been present in blood). Definitions of microbiologic response at the DCIV visit are included in the following table.

Table 11. Study PN003: Definition of Microbiologic Response at the DCIV Visit

Microbiological Response	Response Definition

Eradication	A urine culture taken at the DCIV visit (or, if not available at DCIV, from the last available urine culture after at least 48 hours of IV study therapy), shows that a uropathogen found at study entry at $\geq 10^5$ CFU/mL is reduced to $<10^4$ CFU/mL.
Persistence	A urine culture taken at the DCIV visit (or, if not available at DCIV, from the last available urine culture after at least 48 hours of IV study therapy) grows $\geq 10^4$ CFU/mL of an original uropathogen.
Persistence with acquisition of resistance	A urine culture at the DCIV visit (or, if not available at DCIV, from the last available urine culture after at least 48 hours of IV study therapy) grows $\geq 10^4$ CFU/mL of any uropathogen species that was previously susceptible to imipenem but now has documented resistance to imipenem.
Superinfection	A urine culture grows $\geq 10^5$ CFU/mL of a uropathogen other than a baseline pathogen during the course of IV study therapy OR emergence during IV study therapy of a new pathogen at a distant site along with worsening signs and symptoms of infection.
Indeterminate	a) Follow-up cultures are not available due to subject death or withdrawal from study, OR b) Microbiological data are incomplete, OR c) Assessment not possible due to protocol violation, OR d) Any other circumstance which makes it impossible to define the microbiological response.
DCIV=discontinuation of IV study therapy; IV=intravenous; CFU=colony forming units	

Source: Table 9-3 of Study Report

For follow-up visits, the definitions of microbiological response are included in the following table.

Table 12. Study PN003: Definition of Microbiologic Response at the EFU and LFU Visits

Microbiological Response	Response Definition
Sustained eradication	A urine culture taken at the respective follow-up visit shows that all uropathogens found at study entry at $\geq 10^5$ CFU/mL are still reduced to $<10^4$ CFU/mL.
Persistence	The urine culture taken at the DCIV visit (or, if not available at DCIV, from the last available urine culture after at least 48 hours of IV study therapy) grows $\geq 10^4$ CFU/mL of an original uropathogen. These subjects are carried forward with this status to the 2 follow-up visits.
Persistence with acquisition of resistance	The urine culture at the DCIV visit (or, if not available at DCIV, from the last available urine culture after at least 48 hours of IV study therapy) grows $\geq 10^4$ CFU/mL of any uropathogen species that was previously susceptible to imipenem but now has documented resistance to imipenem. These subjects are carried forward with this status to the 2 follow-up visits.
New infection	A pathogen, other than an original microorganism found at baseline at a level

	≥10^5 CFU/mL, is present in the urine at a level ≥10^5 CFU/mL any time after IV study therapy is finished. If a pathogen is isolated from a site distant to the primary infection after IV study therapy has been completed, then this will also be designated as a new infection. A new infection identified at the EFU will be carried forward to the LFU visit.
Recurrence	A urine culture grows ≥10^4 CFU/mL of an original uropathogen taken any time after documented eradication at DCIV visit. Recurrence identified at the EFU will be carried forward to the LFU visit.
Recurrence with acquisition of resistance	A urine culture, taken any time after documented eradication at the DCIV visit, grows ≥10^4 CFU/mL of an original uropathogen and has documented resistance to imipenem. Recurrence with acquisition of resistance identified at the EFU will be carried forward to the LFU visit.
Indeterminate	a) Follow-up cultures are not available due to subject death or withdrawal from study, OR b) Microbiological data are incomplete, OR c) Assessment not possible due to protocol violation, OR d) Any other circumstance which makes it impossible to define the microbiological response

Source: Table 9-3 of Study Report

We assessed a combined clinical and microbiologic efficacy endpoint (resolution of the symptoms of cUTI at trial entry [and no new symptoms]) and microbiologic response (<10^3 colony forming units [CFU]/mL), consistent with the approach with recent cUTI trials. Note that this endpoint was defined by the Applicant only for the EFU visit as an exploratory endpoint and at the LFU visit as a secondary endpoint.

Secondary endpoints included clinical response. Clinical signs and symptoms of cUTI or acute pyelonephritis, including fever (or history of fever), chills or rigors (accompanied by fever), flank pain, costovertebral angle (CVA) tenderness on physical examination, dysuria, urinary urgency, urinary frequency, suprapubic or pelvic pain, nausea, or vomiting were determined at study entry and planned visits. Signs and symptoms were graded for intensity by the investigator as "none", "mild", "moderate", or "severe". At the DCIV visit, the investigator assessed the clinical response as "cured," "improved," "failure," or "indeterminate" based on comparison to admission signs and symptoms. A favorable clinical response at the DCIV visit included "cured" or "improved."

Table 13. Study PN003: Definition of Clinical Response at the DCIV Visit

Clinical Response	Response Definition
Cure	All pretherapy signs and symptoms of the index infection have resolved (or returned to "preinfection status") AND no additional IV antibiotic therapy is required.
Improved	All or most pretherapy signs and symptoms of the index infection have improved or resolved (or returned to "preinfection status") AND no additional IV antibiotic therapy is required.
Failure	No apparent response to IV study therapy in prestudy signs and

	symptoms: persistence or progression of most or all pretherapy signs and symptoms
Indeterminate	Study data are not available for evaluation of clinical response for any reasons at the DCIV visit, including: a) Complication related to underlying medical condition, OR b) Subject was withdrawn for any reason before sufficient data had been obtained to permit evaluation for any reason, OR c) Extenuating circumstances preclude classification as "cure," "improved," or "failure" OR d) Death occurred during the study period and the index infection was clearly noncontributory.

Source: Table 9-5 of Study Report

At the EFU visit, clinical response included "cure", "failure", and "indeterminate". At the LFU visit, clinical response included "sustained cure", "failure", "relapse", "indeterminate", where "sustained cure" was defined as all or most pretherapy signs and symptoms of the index infection resolved (or returned to "preinfection status") with no evidence of resurgence and no additional antibacterial therapy (beyond IV study therapy and oral ciprofloxacin) was required. Failure at the LFU visit was carried forward from the EFU visit.

Reviewers' comment: The Agency had noted the scientific issues with interpreting as an appropriately designed NI trial and had recommended modifications to the trial design. The Applicant preferred to retain their proposal. The limitations in the design of these studies impair their ability to provide results on which reliable conclusions can be drawn. As designed this is not an adequate and well-controlled trial and is being evaluated for descriptive purposes only.

Key Inclusion and Exclusion Criteria

Inclusion criteria

Inclusion criteria included:

1. Patient was ≥18 years of age.

2. Sexually active females of childbearing potential with a negative urine pregnancy test were eligible for enrollment; however, this must have been followed up with a confirmed negative serum pregnancy test (β-HCG) as soon as possible (within 48 hours of the screening visit).

   A patient who was of reproductive potential agreed to remain abstinent or use (or have their partner use) a medically acceptable effective method of birth control until study completion.

   pyelonephritis judged by the investigator to be serious (requiring hospitalization and treatment with IV antibacterial therapy) according to the following disease definitions:

a) **Acute pyelonephritis** was defined as a systemic, ascending urinary tract infection in a patient with normal urinary tract anatomy, clinically manifested by meeting at least 2 of the following criteria:
   - Fever (defined as ≥38.0°C [≥100.4°F] orally OR an oral equivalent [≥38.5°C (≥101.3°F) by tympanic or rectal measurement])
   - Flank pain
   - CVA tenderness on physical examination
   - Nausea or vomiting

   NOTE: Symptoms of lower UTI (e.g. dysuria, urinary frequency, or urinary urgency) may or may not have been present in acute pyelonephritis.

b) **Complicated UTI** was defined as a clinical syndrome in men or women characterized by the development of at least 2 of the following local or systemic signs and symptoms:

   - Local signs and symptoms: Dysuria, urinary frequency, suprapubic or pelvic pain, or urinary urgency
   - Systemic signs and symptoms: Fever (as defined above), chills or rigors (accompanied by fever), flank pain, or CVA tenderness on physical examination

   The above symptoms must have also occurred in the presence of at least 1 of the following conditions, which increased the risk of developing an infection:

   - Presence of indwelling urinary catheter or other urinary bladder instrumentation
   - Any functional or anatomical abnormality of the urogenital tract (including anatomic malformations or neurogenic bladder) with voiding disturbance resulting in at least 100 mL of residual urine
   - Current obstructive uropathy (nephrolithiasis or fibrosis) that was scheduled to be medically or surgically relieved during IV study therapy
   - Males with documented history of urinary retention (i.e., due to benign prostatic hypertrophy)

3. Patient had pyuria, determined by a midstream clean-catch (MSCC) or catheterized (indwelling or straight catheter) urine specimen with ≥10 WBCs per high-power field on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine.

   NOTE: If pyuria could not be determined by urinalysis in a clinically relevant timeframe, a urine dipstick may have been employed as a rapid diagnostic aid. If urine dipstick was used, a positive test for leukocyte esterase was the preferred indicator for the presence of pyuria. A positive nitrite test was an acceptable indicator of infection.

4. Patient had one positive urine culture within 48 hours of enrollment, as defined below:
    - $\geq 10^5$ CFU/mL of uropathogen either from a MSCC or indwelling catheter urine specimen, OR
    - $\geq 10^4$ CFU/mL of uropathogen either from a MSCC or indwelling catheter urine specimen if blood culture is also positive, OR
    - $\geq 10^2$ CFU/mL of uropathogen from a straight catheter specimen

    NOTE: If more than one pathogen was identified, each should have been present at the colony counts noted above to be considered pathogens. In general, if more than 2 bacterial pathogens were identified in an admission urine culture at the predefined colony counts, the sample should have been considered contaminated (unless one of the pathogens was also identified in a blood culture).

    NOTE: A patient may have been enrolled before the urine culture results were available if it was likely to be positive (based on clinical findings and urinalysis). As described in Patient Exclusion Criteria, culture results must have been available prior to enrollment for those patients receiving prophylactic antibiotics.

Exclusion criteria

Exclusion criteria included:

1. Patient had complete obstruction of any portion of the urinary tract (requiring a permanent indwelling urinary catheter or instrumentation), had a known ileal loop, or had intractable vesico-ureteral reflux.

2. Patient had a cUTI in whom a temporary indwelling urinary catheter was in place and could not be removed at study entry.

    NOTE: All indwelling urinary catheters must have been removed prior to the start of IV study therapy. Unless medically necessary, it was recommended that an indwelling urinary catheter not be reinserted during the study (at least while on IV study therapy).

3. Patient had a perinephric or intrarenal abscess or known or suspected prostatitis.

4. Patient had an uncomplicated UTI (e.g., a female patient with urinary frequency, urgency or pain/discomfort without any risk factors for infection as outlined in Inclusion Criteria #4b).

5. Patient had received any amount of effective antibacterial therapy (defined as therapy known to be active against the identified uropathogen) after obtaining the urine culture for admission to this study (admission urine culture) and prior to the administration of the first dose of IV study therapy. Patient had received any amount of effective

antibiotic therapy (defined as therapy known to be active against the identified uropathogen) after obtaining the urine culture for admission to this study (admission urine culture) and prior to the administration of the first dose of IV study therapy.

6. Patient had an infection which had been treated with >24 hours of systemic antibiotic therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to consideration for entry into the study (only patients with a urine culture positive for the presence of at least 1 gram-negative enteric[s] and/or anaerobic pathogen[s] commonly isolated in UTI were considered microbiologically evaluable).

   NOTE: Patients on prophylactic antibiotic therapy were enrolled only if their admission culture was confirmed to be positive for at least 1 gram-negative enteric(s) and/or anaerobic pathogen(s) commonly isolated in UTI. Culture results must have been available from those patients on prophylactic antibiotics prior to enrollment.

   NOTE: If a patient had received >24 hours of systemic antimicrobial therapy, there must have been clear evidence that the patient had failed this regimen or developed the cUTI while on the previous antibiotic regimen. Such evidence would have included new or continued fever or persistence or worsening of symptoms related to the index infection and persistent positive cultures and persistent laboratory or radiographic changes (if previously present). These measures were confirmed prior to study entry.

7. Patient had a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to carbapenem antibiotics, any cephalosporins, penicillins, or other β-lactam agents.

   NOTE: Patients with history of mild rash to penicillins or other β-lactams may have been enrolled and closely monitored.

8. Patient had a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to other β-lactamase inhibitors (e.g., tazobactam, sulbactam, clavulanic acid).

   NOTE: Patients with history of mild rash to other β-lactamase inhibitors may have been enrolled and closely monitored.

9. Patient had a history of a seizure disorder.

10. Patient was currently being treated with valproic acid or had received treatment with valproic acid in the 2 weeks prior to screening.

11. Patient had a rapidly progressive or terminal illness (unlikely to survive the approximately 6- to 8-week study period).

12. Patient was pregnant or expecting to conceive, was breast feeding, or planned to breast feed during participation in the study.

13. Patient in whom a response to all study therapy (IV study therapy or subsequent oral ciprofloxacin) within the timeframe of treatment specified in this protocol was considered unlikely.

14. Patient had a concurrent infection that would have interfered with evaluation of response to the study antibiotics (IMI with or without MK-7655).

15. Patient had a need for concomitant systemic antimicrobial agents in addition to those designated in the various study treatment groups.

    NOTE: Use of IV vancomycin to treat confirmed or suspected methicillin-resistant S. aureus (MRSA) infection or use of daptomycin or linezolid to treat confirmed or suspected MRSA or vancomycin-resistant *Enterococcus spp.* (VRE) infection was allowed.

16. Patient had a cUTI due to a confirmed fungal pathogen.

    NOTE: Use of antifungal therapy for treatment of mucocutaneous infections (e.g., vaginal candidiasis onychomycosis) was allowed.

17. Patient was currently receiving immunosuppressive therapy, including use of high-dose corticosteroids (i.e., >40 mg prednisone or prednisone equivalent per day).

    NOTE: Prior short-term use (≤5 days) of steroid therapy in the 30 days prior to study entry was allowed.

18. Patient was a prior recipient of a renal transplantation.

19. Patient had estimated or actual creatinine clearance of ≤5 mL/min, or was currently undergoing hemodialysis.

20. The patient had any of the following laboratory abnormalities at the time of screening:

    - ALT values ≥ 3 times the upper limit of normal (ULN)
    - AST values ≥ 3 times ULN
    - ALT or AST ≥ 2 times ULN accompanied by total bilirubin (BILI) >ULN
    - Total BILI value ≥ 2 times ULN

    NOTE: Patients with acute hepatic failure or acute decompensation of chronic hepatic failure were also excluded.

Statistical Analysis Plan

Analysis Populations

Microbiological intention-to-treat (MITT) Population: The MITT population included those subjects who met both of the following two conditions:

1. The subject received at least one dose of IV study therapy.

2. The pre-study urine culture grew a gram-negative and/or anaerobic pathogen at any quantity, regardless of the susceptibility of the uropathogen.

This population was used by the Applicant in a supportive analysis of the primary efficacy endpoint. The MITT population will be considered as the primary analysis population. Additionally, we have considered susceptibility to the control, IMI, in defining the MITT population as discussed in the results section below.

Microbiologically-evaluable (ME) Population: This population excluded subjects due to important deviations from the protocol that may have substantially affected the results of the primary efficacy endpoint. Reasons for exclusion from the ME population included the following:

1. The subject failed to meet the protocol definition of cUTI.

2. The subject's pre-study urine culture failed to grow a gram-negative and/or anaerobic pathogen at sufficient quantity specified in the Inclusion Criteria (i.e., growth at $<10^5$ CFU/mL of uropathogen for a MSCC or indwelling catheter urine specimen OR $<10^4$ CFU/mL of uropathogen if blood culture is also positive OR $<10^2$ CFU/mL of uropathogen for a straight catheter specimen).

3. The subject had significant violations of inclusion/exclusion criteria that could impact on the efficacy assessment (e.g., receipt of previous or concurrent systemic antibacterial therapy beyond those allowed per protocol).

4. The subject received less than 96 hours of IV study therapy (16 infusions if q6h dosing or 12 infusions if q8h dosing), except for subjects who switched IV therapy due to unfavorable clinical and microbiological responses after at least 72 hours of IV study therapy.

Additionally, subjects with indeterminate results were excluded from the analysis of the ME population. The ME population was used by the Applicant for the primary efficacy analysis. Using this analysis population for the primary analysis is not acceptable because of the

exclusion of subjects based on post-randomization information (such as duration of IV therapy, indeterminate response) which might be related to treatment.

Analysis Methods

Sample Size Calculation: With 100 subjects randomized into each group, the statistical power was 0.87, using an overall one-sided 2.5% alpha level, a noninferiority (NI) margin of -15% (REL minus control), an underlying response rate of 95% for the control regimen and the investigational regimen, a microbiological evaluability rate (in the ME population) of 60%, and an asymptotic method proposed by Miettinen and Nurminen.

Primary Efficacy Analysis: For the primary efficacy analysis, 95% confidence intervals (CIs) of between-treatment differences (REL minus control) and p-values were calculated using the Miettinen and Nurminen method. The study was designed with an NI margin of 15%. If NI for either dose group of REL relative to control was established, then a subsequent test was performed to determine whether or not that dose level of REL was superior to the control regimen. Note that the cUTI guidance considers a 10% NI margin acceptable for this indication based on both historical data and clinical judgment. Additionally, for an NI assessment to be interpretable, it is necessary that the control drug be effective. In this review, the MITT population will exclude subjects with infection due to organisms that are resistant to the control when NI testing is conducted.

The Type I error rate over the multiple treatment comparisons was controlled by the pre-specified closed testing procedure, comparing the REL 250-mg regimen to control first, followed by comparison of the REL 125-mg regimen to control.

The efficacy analysis in the MITT population considered subjects with "indeterminate" assessments as having an unfavorable response.

Three interim analyses were conducted to evaluate the safety and tolerability of the investigational drug. No efficacy analyses were conducted at any of the interim analyses; however, protocol-specific summary statistics for key efficacy endpoints were provided to help in the assessment of benefit-to-risk.

Protocol Amendments

Six amendments were made. The changes included removal of future biomedical research information and procedures in Brazil, revision and subsequent removal of inclusion criterion #3 (presence of at least 1 of 3 risk factors for infection with an antibacterial-resistant organism). These changes were not expected to affect assessment of efficacy.

Compliance with Good Clinical Practices

This study was performed in compliance with Good Clinical Practices.

Financial Disclosure

No financial interests were disclosed in the submission.

Patient Disposition

The study was conducted between December 2012 and July 2015, with subjects enrolled at 35 centers in 11 countries (Bulgaria, Greece, Korea, Latvia, Peru, Poland, Romania, Russia, Turkey, Ukraine, and United States). A total of 302 subjects from 34 centers were randomized 1:1:1 into one of the three treatment groups. The patient disposition information is presented in the following table. Four subjects were randomized but not treated: two in the 250-mg group (physician's decision or withdrawal by subject) and two in the 125-mg group (protocol violation). The majority of subjects completed the study and study medication (over 90% of subjects in each treatment arm completed study/study drug). The reasons for discontinuation of study or study medication were similar between the three groups. Four subjects were switched to high dose REL because of early unfavorable clinical outcome. These subjects were considered treatment failures in the analysis.

Table 14. Study PN003: Study Disposition

	IMI/REL 250 mg n (%)	IMI/REL 125 mg n (%)	IMI/Placebo n (%)	Total n (%)
Randomized	101 (100)	101 (100)	100 (100)	302 (100)
Randomized but not treated	2 (2)	2 (2)	0	4 (1.3)
Treated with any study therapy	99 (98)	99 (98)	100 (100)	298 (98.7)
Switched to high dose	1(1)	2(2)	1 (1)	4 (1.3)
Completed study medication	94 (93.1)	94 (93.1)	95 (95)	283 (93.7)
Discontinued study medication	5 (5)	5 (5)	4 (4)	14 (4.6)
Adverse event	3 (3)	1 (1)	2 (2)	6 (2)
Physician decision	0 (0)	1 (1)	0	1 (0.3)
Technical problems†	1 (1)	2 (2)	1 (1)	4 (1.3)
Withdrawal by subject	1 (1)	1 (1)	1 (1)	3 (1)
Completed study	92 (91.1)	91 (90.1)	94 (94)	277 (91.7)
Discontinuation from study	9 (8.9)	10 (9.9)	5 (5)‡	24 (7.9)
Adverse event	1 (1)	0 (0)	0	1 (0.3)
Death	1 (1)	0 (0)	0	1 (0.3)
Loss to follow-up	1 (1)	4 (4)	4 (4)	9 (3)
Physician decision	1 (1)	1 (1)	0	2 (0.7)
Protocol violation	2 (2)	0 (0)	0	2 (0.7)
Technical problems†	1 (1)	0	0	1 (0.3)
Withdrawal by subject	2 (2)	5 (5)	1 (1)	8 (2.6)
MITT Population§	74 (73.3)	82 (81.2)	81 (81)	237 (78.5)
Exclusion from MITT	27 (26.7)	19 (18.8)	19 (19)	65 (21.5)
Reasons for exclusion				

Baseline culture not meeting protocol-specific requirements	25 (24.8)	17 (16.8)	19 (19)	61 (20.2)
Not receiving IV study therapy	2 (2)	2 (2)	0	4 (1.3)
ME population at DCIV	67 (66.3)	71 (70.3)	75 (75)	213 (70.5)
MITT subjects exclued from ME at DCIV	7 (6.9)	11 (10.9)	6 (6)	24 (7.9)
Reasons for exclusion				
Inadequate duration of IV study therapy	2 (2)	2 (2)	1 (1)	5 (1.7)
Incorrect IV study therapy	1 (1)	1 (1)	0	2 (0.7)
Subjects with indeterminate response at DCIV*	4 (4)	8 (7.9)	5 (5)	17 (5.6)

Note: Percentages were based on number of subjects randomized.
*The numbers of subjects in the ME population for the analysis of EFU were 65, 72, and 71 and for the analysis of LFU were 63, 69, and 72, for the three treatment groups. The differences in sample size were due to different numbers of subjects with indeterminate results at EFU and LFU.
‡ One subject (ID: (b) (6), IMI+Placebo group) completed the EFU visit, but not the LFU visit, and should have been listed as a discontinuation.
+Subjects discontinued due to insufficient supply of study drug at site.
§ An additional 10 and 6 subjects with resistance to the control (IMI) were excluded from the MITT population from the REL 250 mg arm and control arm for NI testing.

A total of 78.5% and 76.2% of randomized subjects were included in the MITT and ME populations, respectively. The majority (61/65 or 94%) of the exclusions from the MITT population were due to subject's baseline culture not meeting protocol-specified requirements. A higher proportion of subjects in the 250-mg group were excluded for this reason than in other two groups. Among 24 MITT subjects excluded from the ME population, the reasons for exclusions were similar.

The following table reports the duration of IV therapy and total therapy. The REL 250-mg group had the shortest treatment duration of the three groups. Note that 49 subjects (16%) switched to oral therapy and the numbers were balanced across the three arms.

Table 15. Study PN003: Treatment Duration (All Treated Subjects)

	IMI/REL 250 mg N=99 n (%)	**IMI/REL 125 mg N=99 n (%)**	**IMI/Placebo N=100 n (%)**	**Total N=298 n (%)**
IV therapy duration (days)				
Mean	7.43	8.29	8.23	7.98
SD	2.63	2.95	2.8	2.82
Median	6.8	7.8	7.8	7.7
Range	1.7, 13.8	0.5, 13.8	1.5, 13.8	0.5, 13.8
All therapy duration (days)				
Mean	8.28	9.09	8.93	8.77
SD	2.95	3.01	2.96	2.98
Median	7.8	8.8	8.5	8.5

Range	1.7, 13.8	0.5, 13.9	1.5, 16.5	0.5, 16.5

A summary of the timing of visits since first treatment is shown in the following table. The majority of subjects (98.7%) completed the DCIV visit. The mean time of the DCIV visit was 8.4 days with subjects on the REL 250-mg arm having an assessment almost 1 day on average earlier than the other two arms. The mean time of the EFU visit was 16.3 days and was also slightly earlier in the REL 250-mg arm.

Table 16. Study PN003: Timing of Visits in Days from the First Treatment in the MITT Population

Visit		IMI/REL 250 mg N=74 n (%)	IMI/REL 125 mg N=82 n (%)	IMI/Placebo N=81 n (%)	Total N=237 n (%)
DCIV	N (%)	72 (97.3)	81 (98.8)	81 (100)	234 (98.7)
	Mean	7.8	8.6	8.6	8.4
	SD	2.4	2.8	2.7	2.6
	Median	7.0	8.0	8.0	8.0
	Range	4.0, 14.0	4.0, 14.0	4.0, 14.0	4.0, 14.0
EFU	N (%)	72 (97.3)	79 (96.3)	80 (98.8)	231 (97.5)
	Mean	16.0	16.3	16.5	16.3
	SD	3.4	3.5	3.7	3.5
	Median	15.0	16.0	16.0	16.0
	Range	9.0, 30.0	10.0, 25.0	12.0, 35.0	9.0, 35.0
LFU	N (%)	71 (95.9)	75 (91.5)	78 (96.3)	224 (94.5)
	Mean	42.5	42.0	43.8	42.8
	SD	5.2	5.5	6.1	5.6
	Median	41.0	41.0	42.0	42.0
	Range	35.0, 54.0	30.0, 57.0	33.0, 70.0	30.0, 70.0

Protocol Violations/Deviations

Overall, 45 (14.9%) subjects in the MITT population had protocol deviations. These appeared to be mostly minor deviations which were fairly balanced across the arms.

Demographic Characteristics

In the MITT population, slightly more females were in the REL groups than males, to the contrary of the placebo control group. The majority of subjects were white and about 40% of subjects were 65 years old or older. Most of the subjects (91.1%) were from Europe.

Table 17. Study PN003: Demographic Characteristics in the MITT Population

	IMI/REL 250 mg N=74 n (%)	IMI/REL 125 mg N=82 n (%)	IMI/Placebo N=81 n (%)	Total N=237 n (%)
Gender				

Male	35 (47.3)	35 (42.7)	44 (54.3)	114 (48.1)
Female	39 (52.7)	47 (57.3)	37 (45.7)	123 (51.9)
Race				
American Indian or Alaska Native	2 (2.7)	3 (3.7)	0	5 (2.1)
Asian	1 (1.4)	5 (6.1)	1 (1.2)	7 (3.0)
Multi-racial	3 (4.1)	3 (3.7)	4 (4.9)	10 (4.2)
White	68 (91.9)	71 (86.6)	76 (93.8)	215 (90.7)
Age group (years)				
<65	47 (63.5)	50 (61.0)	46 (56.8)	143 (60.3)
≥65	27 (36.5)	32 (39.0)	35 (43.2)	94 (39.7)
Age group (years)				
18 to 40	14 (18.9)	15 (18.3)	21 (25.9)	50 (21.1)
41 to 64	33 (44.6)	35 (42.7)	25 (30.9)	93 (39.2)
65 to 74	19 (25.7)	18 (22.0)	21 (25.9)	58 (24.5)
≥75	8 (10.8)	14 (17.1)	14 (17.3)	36 (15.2)
Age (years)				
Mean (SD)	55.7 (17.2)	57.2 (17.1)	55.3 (19.7)	56.1 (18.0)
Median	58.5	60.0	61.0	59.0
Range	18, 90	19, 84	18, 86	18, 90
Weight (kg)				
<70	24 (32.4)	29 (35.4)	23 (28.4)	76 (32.1)
≥70	49 (66.2)	52 (63.4)	58 (71.6)	159 (67.1)
Missing	1 (1.4)	1 (1.2)	0	2 (0.8)
Weight (kg)				
N	73	81	81	235
Mean (SD)	75.6 (13.5)	76.2 (17.0)	76.0 (14.6)	75.9 (15.1)
Median	75.6	78.0	75.6	76.0
Range	50.5, 113.4	47.0, 155.0	38.0, 110.0	38.0, 155.0
Region				
Asia Pacific	1 (1.4)	2 (2.4)	1 (1.2)	4 (1.7)
Europe	66 (89.2)	74 (90.2)	76 (93.8)	216 (91.1)
North America	2 (2.7)	0	0	2 (0.8)
South America	5 (6.8)	6 (7.3)	4 (4.9)	15 (6.3)

Other Baseline Characteristics

The following table shows other baseline characteristics. Only a few subjects had indwelling catherization (4 with Foley catheter and 3 with other). The most common urinary tract abnormalities were residual urine (17.7%) and nephrolithiasis (14.3%). Acute pyelonephritis and cUTI were almost evenly distributed across the treatment groups. Only 6.3% of the subjects had bacteremia.

Table 18. Study PN003: Baseline Disease Characteristics in the MITT Population

	IMI/REL 250 mg N=74 n (%)	IMI/REL 125 mg N=82 n (%)	IMI/Placebo N=81 n (%)	Total N=237 n (%)

Baseline pathogen*				
Citrobacter freundii	1 (1.4)	0 (0)	2 (2.5)	3 (1.3)
Enterobacter aerogenes	1 (1.4)	0 (0)	0 (0)	1 (0.4)
Enterobacter cloacae	3 (4.1)	3 (3.7)	3 (3.7)	9 (3.8)
Escherichia coli	51 (68.9)	60 (73.2)	52 (64.2)	163 (68.8)
Klebsiella pneumoniae	8 (10.8)	11 (13.4)	17 (21.0)	36 (15.2)
Pseudomonas aeruginosa	5 (6.8)	7 (8.5)	5 (6.2)	17 (7.2)
Other	14 (18.9)	11 (13.4)	15 (18.5)	40 (16.9)
Indwelling catheterization				
Foley catheter	0	1 (1.2)	3 (3.7)	4 (1.7)
Other	1 (1.4)	1 (1.2)	1 (1.2)	3 (1.3)
Intermittent catheter				
Acute	1 (1.4)	1 (1.2)	1 (1.2)	3 (1.3)
Chronic	0	0	1 (1.2)	1 (0.4)
Urinary tract abnormalities				
Cystocele	0	2 (2.4)	0	2 (0.8)
Hydronephrosis	3 (4.1)	5 (6.1)	3 (3.7)	11 (4.6)
Nephrolithiasis	7 (9.5)	13 (15.9)	14 (17.3)	34 (14.3)
Neurogenic bladder	6 (8.1)	2 (2.4)	2 (2.5)	10 (4.2)
Other	11 (15.5)	6 (7.3)	11 (13.6)	28 (11.8)
Residual urine	11 (15.5)	12 (14.6)	19 (23.4)	42 (17.7)
Vesicoureteral reflux	1 (1.4)	0 (0)	3 (3.7)	4 (1.7)
Ureteropelvic junction obstruction	0	1 (1.2)	0	1 (0.4)
Primary diagnosis				
cUTI	37 (50.0)	40 (48.8)	43 (53.1)	120 (50.6)
Acute pyelonephritis	37 (50.0)	42 (51.2)	38 (46.9)	117 (49.4)
Bacteremia				
Yes	4 (5.4)	7 (8.5)	4 (4.9)	15 (6.3)
No	70 (94.6)	75 (91.5)	77 (95.1)	222 (93.7)
Resistance to imipenem				
Yes	10 (13.5)	9 (11)	6 (7.4)	25 (10.5)
No	64 (86.5)	73 (89)	75 (92.6)	212 (89.5)

*One subject may have more than one baseline pathogen

Reviewer comment: The demographic characteristics were well-balanced between the different treatment groups with the exception of racial and geographic diversity. The majority of patients were white and from Europe, which is not representative of the target population in the United States. There were more female subjects overall, which is consistent with the expected population of cUTI. Demographic characteristics were similar between the ME and MITT populations. The proportion of subjects with urinary tract abnormalities is expected in cUTI.

Treatment Compliance and Concomitant Medications

Compliance was measured by comparing the number of completed study medication doses (IV and oral) to the number of expected. The mean compliance percentages for both IV and oral doses were higher than 93% in each treatment group. Overall, 83.6% of the treated patients completed the treatment with IV doses only and 16.4% continued with oral ciprofloxacin. All groups had similar compliance percentages.

Concomitant Therapy

Overall, 57% of the subjects in the MITT population received specific concomitant therapies. The most common concomitant therapies were for the nervous system, the cardiovascular system, and the alimentary tract and metabolism. The following table shows the number (%) of subjects with specific anti-infective therapies. A higher proportion of the subjects in the 250-mg group received concomitant antibacterial therapy. The review team evaluated the impact this use might have had on the clinical and microbiological response by reviewing the CRFs of each subject receiving concomitant therapy and concluded that in the majority of subjects receiving concomitant anti-infective therapy the efficacy results at the DCIV and EFU visits were not affected based on criteria such as spectrum of the drug, route of administration and timing of administration. There were two patients identified with a favorable response at the EFU visit, one each in the 250-mg REL and placebo arms and six and two subjects in the 250-mg REL and placebo arms at the LFU visit, in whom the concomitant therapy could have affected the outcome.

Table 19. Study PN003: Concomitant Antibacterial Therapies in the MITT Population

	IMI/REL 250 mg N=99 n (%)	IMI/REL 125 mg N=99 n (%)	IMI/Placebo N=100 n (%)	Total N=298 n (%)
Subjects with no systemic anti-infective concomitant therapy	88 (88.9)	96 (97.0)	97 (97.0)	281 (94.3)
Subjects with anti-infectives for systemic use	11 (11.1)	3 (3.0)	3 (3.0)	17 (5.7)
Amikacin	1 (1.4)	1 (1.3)	1 (1.3)	3 (1.3)
Ceftazidime	0	1 (1.3)	0	1 (0.4)
Ceftriaxone sodium	0	1 (1.3)	0	1 (0.4)
Ciprofloxacin	2 (2.8)	0	0	2 (0.9)
Fosfomycin tromethamine	1 (1.4)	0	0	1 (0.4)
Gentamicin	1 (1.4)	0	1 (1.3)	2 (0.9)
Imipenem	2 (2.8)	0	0	2 (0.9)
Levofloxacin	2 (2.8)	0	0	2 (0.9)
Metronidazole	1 (1.4)	0	0	1 (0.4)
Nitrofurantoin	0	1 (1.3)	0	1 (0.4)
Sulfamethoxazole (+) trimethoprim	1 (1.4)	0	0	1 (0.4)
Vancomycin	0	0	1 (1.3)	1 (0.4)

One subject in the second group took two drugs.

Efficacy Results

FDA's Analysis Clinical-Microbiological Response in MITT Population

The following table shows the results for the MITT population at the three assessment time points. The 250-mg REL group had an 85.1% favorable proportion compared to 92.6% on control at the DCIV visit. The results did show a lower success proportion at both the DCIV and EFU visit, but similar proportions at the LFU visit for the REL 250-mg group compared to control.

Table 20. Study PN003: Favorable Clinical-Microbiological Response by Visit in the MITT Population

Visit	IMI/REL 250 mg N=74 n (%)	IMI/REL 125 mg N=82 n (%)	IMI/Placebo N=81 n (%)	Difference (95% CI) (%) REL 250 mg – Placebo REL 125 mg –Placebo
DCIV	63 (85.1)	71 (86.6)	75 (92.6)	-7.5 (-18.3, 2.6) -6 (-16.1, 3.7)
EFU	40 (54.1)	49 (59.8)	50 (61.7)	-7.7 (-22.9, 7.9) -2.0 (-16.8, 13.0)
LFU	40 (54.1)	44 (53.7)	44 (54.3)	-0.3 (-15.8, 15.3) -0.7 (-15.8, 14.5)

95% CIs of between-treatment differences were based on unconditional asymptotic Miettinen and Nurminen method.

For an NI assessment of IMI/REL 250 mg, we excluded 16 subjects (10 in the test arm and 6 in the control arm) whose baseline isolates were resistant to imipenem. The baseline pathogens were *Morganella morganii* (4), *Proteus mirabili*s (2), *Proteus vulgaris* (1), *Providencia rettgeri* (1), and *Pseudomonas aeruginosa* (2) in the 250-mg group; Acinetobacter *baumannii* complex (2), *Klebsiella pneumoniae* (1), *Proteus mirabilis* (1), and *Pseudomonas aeruginosa* (2) in the placebo group. The 250-mg REL group had an 83% favorable proportion compared to 92% on control at the DCIV visit with a 95% CI of [-21.3%, 1.9%]. The lower bound of the 95% CI was -21.3% meaning that the 250-mg REL group could be as much as 21.3% worse than the control group. These results do not support the NI of IMI/REL 250-mg group to control. In general, a 10% NI margin is recommended for cUTI trials and a 15% NI margin has been considered acceptable for a limited use indication when the drug addresses an unmet need. However, as noted previously this study was not designed or powered to be able to make this NI assessment.

An analysis using 10^3 CFU/mL would only change the microbiological results for two subjects in the placebo group (each at the EFU or LFU visits) and does not change the overall conclusions of the analysis.

Applicant's Primary Analysis: Microbiological Response in ME Population

The Applicant's primary efficacy analysis of microbiological response at the DCIV visit in the ME population is shown in the following table. All subjects with missing/indeterminate assessment were excluded from the analysis. We do not agree with this analysis, due to the use of the ME population and the exclusion of subjects with missing/indeterminate assessment.

Table 21. Study PN003: Microbiological Favorable Response by Visit in the ME population

Visit	IMI/REL 250 mg	IMI/REL 125 mg	IMI/Placebo	Difference (95% CI) REL 250 mg – Placebo REL 125 mg – Placebo
DCIV	64/67 (95.5)	70/71 (98.6)	74/75 (98.7)	-3.1 (-11.2, 3.2) -0.1 (-6.4, 5.9)
EFU	40/65 (61.5)	49/72 (68.1)	50/71 (70.4)	-8.9 (-24.6, 7.1) -2.4 (-17.4, 12.8)
LFU	43/63 (68.3)	45/69 (65.2)	45/72 (62.5)	5.8 (-10.4, 21.5) 2.7 (-13.1, 18.4)

95% CIs of between-treatment differences were based on unconditional asymptotic Miettinen and Nurminen method.
The exact 95% CI for the difference between the 250-mg group and the placebo at the DCIV visit was [-11.3%, 3.4%]; and between the 125-mg group and the placebo was [-6.2%, 6.4%], calculated by the reviewer due to the small number of failures at the DCIV and EFU visits.

Microbiological Response by Visit in the MITT Population

The following table shows the proportion of favorable microbiological responses using a 10^4 CFU/mL cut-off point for eradication, as defined in the protocol, in subjects in the MITT population. As with the results above, the microbiological response rates were slightly lower in the REL groups than in the control group at both the DCIV and EFU visits.

Table 22. Study PN003: Favorable Microbiological Response by Visit in the MITT Population

Visit	Response	IMI/REL 250 mg N=74	IMI/REL 125 mg N=82	IMI/Placebo N=81	Difference (95% CI) REL 250mg – Placebo REL 125 mg – Placebo
DCIV	Favorable	65 (87.8)	72 (87.8)	75 (92.6)	-4.8 (-15.1, 4.9) -4.8 (-14.7, 4.7)
	Unfavorable	3 (4.1)	1 (1.2)	1 (1.2)	
	Indeterminate	6 (8.1)	9 (11.0)	5 (6.2)	
EFU	Favorable	41 (55.4)	51 (62.2)	51 (63.0)	-7.6 (-22.8, 7.9) -0.8 (-15.5, 14.0)
	Unfavorable	24 (32.4)	21 (25.6)	20 (24.7)	
	Indeterminate	9 (12.2)	10 (12.2)	10 (12.3)	
LFU	Favorable	44 (59.5)	46 (56.1)	46 (56.8)	2.7 (-12.8, 18.0) -0.7 (-15.8, 14.4)
	Unfavorable	21 (28.4)	23 (28.0)	26 (32.1)	
	Indeterminate	9 (12.2)	13 (15.9)	9 (11.1)	

95% CIs of between-treatment differences were based on unconditional asymptotic Miettinen and Nurminen method.

Clinical Response by Visit in the MITT Population

The cure proportions in clinical response were comparable (90.5% to 92.7%) in the three treatment groups at the DCIV visit. The 250-mg REL group was numerically lower than the control group at the EFU visit and LFU visit.

Table 23. Study PN003: Clinical Response by Visit in the MITT Population

Visit		IMI/REL 250 mg N=74 n (%)	IMI/REL 125 mg N=82 n (%)	IMI/Placebo N=81 n (%)	Difference (95% CI) REL 250mg – Placebo REL 125mg - Placebo
DCIV	Cure	67 (90.5)	74 (90.2)	76 (92.7)	-3.3 (-13.0, 5.6) -3.6 (-12.8, 5.3)
	Improved	3 (4.1)	6 (7.3)	5 (6.1)	
	Failure	1 (1.4)	0	0	
	Missing	2 (2.7)	1 (1.2)	0	
	Indeterminate	1 (1.4)	1 (1.2)	0	
EFU	Cure	60 (81.1)	69 (84.1)	72 (88.9)	-7.8 (-19.4, 3.5) -4.7 (-15.7, 6.1)
	Failure	6 (8.1)	6 (7.3)	4 (4.9)	
	Missing	3 (4.1)	3 (3.7)	1 (1.2)	
	Indeterminate	5 (6.8)	4 (4.9)	4 (4.9)	
LFU	Sustained Cure	59 (79.7)	65 (79.3)	69 (85.2)	-5.5 (-17.9, 6.7) -5.9 (-17.9, 6.0)
	Failure	5 (6.8)	2 (2.4)	3 (3.7)	
	Missing	3 (4.1)	7 (8.5)	3 (3.7)	
	Indeterminate	6 (8.1)	2 (2.4)	1 (1.2)	
	Relapse	1 (1.4)	6 (7.3)	5 (6.2)	

95% CIs of between-treatment differences were based on unconditional asymptotic Miettinen and Nurminen method.

Findings in Special/Subgroup Populations or Additional Analyses Conducted on the Individual Trial

Gender, Race, Age, Weight, Country, and Baseline Disease Characteristics

The following table shows FDA's clinical and microbiological outcome at the DCIV visit by baseline variables in the MITT population. Males had a lower proportion of favorable outcome in the 250-mg group than in the placebo group; while females had a similar response in the 250-mg group and in the placebo group. In general, when the sample size was large enough, the 250-mg group had a poorer outcome, consistent with the trend for all MITT subjects. Prior effective antibacterial therapy did not appear to impact efficacy responses. Among those patients with a favorable clinical and microbiological response at DCIV, use of prior effective antibacterial therapy was reported only in one patient who received fosfomycin prior to enrollment.

Table 24. Study PN003: Subgroup Analysis of Favorable Clinical and Microbiological Response at DCIV in the MITT Population

	IMI/REL 250 mg N=74 n (%)	IMI/REL 125 mg N=82 n (%)	IMI/Placebo N=81 n (%)
All subjects	63 (85.1)	71 (86.6)	75 (92.6)
Gender			
Male	28/35 (80.0)	31/35 (88.6)	42/44 (95.5)
Female	35/39 (89.7)	40/47 (85.1)	33/37 (89.2)
Race			
American Indian or Alaska Native	1/2 (1)	3/3 (100)	0
Asian	1/1 (100)	4/5 (80)	0/1 (0)
Multi-racial	1/3 (1)	2/3 (66.7)	3/4 (75)
White	60/68 (60)	62/71 (87.3)	72/76 (94.7)
Age (years)			
<65	40/47 (85.1	44/50 (88)	42/46 (91.3)
≥65	23/27 (85.2)	27/32 (84.4)	33/35 (94.3)
Region			
Asia & Pacific	1/1 (100)	1/2 (50)	0/1 (0)
Europe	59/66 (89.4)	65/74 (87.8)	72/76 (94.7)
South America	2/5 (40)	5/6 (83.3)	3/4 (75)
US/Canada	1/2 (50)	0	0
Primary diagnosis			
Pyelonephritis	31/37 (83.8)	37/42 (88.1)	34/38 (89.5)
cUTI	32/37 (86.5)	34/40 (85)	41/43 (95.3)
Bacteremia			
Yes	3/4 (75)	6/7 (85.7)	3/4 (75)
No	60/70 (85.7)	65/75 (86.7)	72/77 (93.5)
Resistance to imipenem			
Yes	10/10 (100)	7/9 (77.8)	6/6 (100)
No†	53/64 (82.8)	64/73 (87.7)	69/75 (92)
Prior systemic anti-infective use			
Yes	4/5 (80)	5/7 (71.4)	5/6 (83.3)
No	59/69 (85.5)	66/75 (88)	70/75 (93.3)

†The difference and its 95% CI between the REL 250-mg group and placebo group in the imipenem-susceptible subjects were -9.2% [-21.3%, 1.9%], based on unconditional asymptotic Miettinen and Nurminen method.

Table 25. Study PN003: Favorable Clinical and Microbiological Response by Baseline Pathogen in the MITT Population

	IMI/REL 250 mg N=74 n (%)	IMI/REL 125 mg N=82 n (%)	IMI/Placebo N=81 n (%)
DCIV			

Citrobacter freundii	1/1 (100)	0	2/2 (100)
Enterobacter aerogenes	1/1 (100)	0	0
Enterobacter cloacae	3/3 (100)	3/3 (100)	3/3 (100)
Escherichia coli	44/51 (86.3)	54/60 (90.0)	49/52 (94.2)
Klebsiella pneumoniae	8/8 (100)	10/11 (90.9)	16/17 (94.1)
Pseudomonas aeruginosa	4/5 (80.0)	6/7 (85.7)	5/5 (100)
Other	13/14 (92.9)	9/11 (81.8)	15/15 (100)
EFU			
Citrobacter freundii	1/1 (100)	0	0/2 (0)
Enterobacter aerogenes	1/1 (100)	0	0
Enterobacter cloacae	2/3 (66.7)	2/3 (66.7)	0/3 (0)
Escherichia coli	29/51 (56.9)	37/60 (61.7)	35/52 (67.3)
Klebsiella pneumoniae	4/8 (50.0)	6/11 (54.5)	10/17 (58.8)
Pseudomonas aeruginosa	1/5 (20.0)	2/7 (28.6)	2/5 (40.0)
Other	7/14 (50)	6/11 (54.5)	10/15 (66.7)
LFU			
Citrobacter freundii	1/1 (100)	0	0/2 (0)
Enterobacter aerogenes	1/1 (100)	0	0
Enterobacter cloacae	3/3 (100)	1/3 (33.3)	0/3 (0)
Escherichia coli	29/51 (56.9)	32/60 (53.3)	34/52 (65.4)
Klebsiella pneumoniae	4/8 (50.0)	8/11 (72.7)	8/17 (47.1)
Pseudomonas aeruginosa	0/5 (0)	2/7 (28.6)	2/5 (40.0)
Other	7/14 (50)	4/11 (36.4)	8/15 (53.3)

Efficacy Conclusions

As this study is primarily considered a descriptive study, it is difficult to make any conclusions regarding efficacy. However, there were some trends of concern. The combined microbiological and clinical endpoint showed numerically lower success rates at the DCIV and EFU visits for REL 250 mg compared to control. The lower rates at the DCIV visit were driven by the microbiological component of the endpoint while the lower rates at the EFU visit were seen with both clinical and microbiologic components.

This study was not designed to provide evidence of the added contribution of REL 250 mg to IMI. It was also not designed to provide a scientifically sound NI assessment of IMI/REL 250 mg to IMI alone using an appropriate analysis population and endpoint. Even if the study were assessed as a well-designed NI trial, using the appropriate analysis population and endpoints, the trial does not meet an acceptable NI margin, even for a limited use indication. From a clinical standpoint, an NI trial comparing IMI/REL to IMI provides limited information in that it shows that the addition of REL 250 mg does not reduce the efficacy of IMI greater than what would be considered acceptable for a new treatment for cUTI. An NI trial comparing IMI/REL to another appropriate comparator would also be limited in its ability to demonstrate the added contribution of REL; however, it could have allowed for the inclusion of subjects with infection

due to imipenem-resistant organisms, thus allowing for a better assessment of relebactam's ability to restore the activity of imipenem against imipenem nonsusceptible pathogens.

7.3.2 Study PN004 (cIAI)

Trial Objectives

The main study objectives were to evaluate the safety and tolerability and to assess the efficacy of doses of IMI/REL versus IMI alone in patients with cIAI.

The primary objectives were

1. To evaluate the efficacy of two doses of REL (250 mg and 125 mg) plus IMI, as compared with IMI alone, with respect to the clinical response assessment profile in the treatment of adult subjects with cIAI at completion of IV study therapy (DCIV).

2. To evaluate the safety and tolerability profile of two doses of REL (250 mg and 125 mg) plus IMI

Trial Design and Endpoints

This was a multicenter, randomized, double-blind, active comparator-controlled clinical trial in adults 18 years old or older.

Eligible subjects based upon inclusion and exclusion criteria were randomized in a 1:1:1 ratio to receive IV study therapy of REL (250 mg) plus IMI (500 mg) (Treatment Group 1), REL (125 mg) + IMI (500 mg) (Treatment Group 2), or IMI (500 mg) plus matching placebo (normal saline) for REL (Treatment Group 3). The administration was every 6 hours (q6h) IV. Dose adjustments for patients with renal impairment and/or low body weight were the same as in PN003.

The total duration of IV therapy was 4 to 14 days. There was no option to switch to oral therapy. Subjects were evaluated daily while on IV study therapy for safety and tolerability. Two follow-up visits occurred 5 to 9 days after IV study therapy (EFU) and 28 to 42 days after IV study therapy (LFU). The third follow-up visit occurred at Day 28 (+7 days) post-randomization (global follow-up [GFU]). Clinical response and safety were evaluated at the DCIV, EFU, and LFU visits. A global response rating (described below) was performed at the GFU visit as an exploratory endpoint.

This study was double-blind under in-house blinding procedures. The results of the planned interim analyses were not shared with the investigators prior to the completion of the study. Subject-level unblinding and treatment level results were restricted to the unblinded (or designated) statistician who prepared the interim analysis and who had no other responsibility associated with the study.

Clinical response at the DCIV visit was the primary efficacy endpoint in the Applicant's analysis. For NI trials in cIAI, a primary endpoint of clinical success defined as resolution of the baseline signs and symptoms of cIAI based on objective assessments of events from randomization until approximately day 28 is recommended. We considered the GFU visit at day 28 for our assessment as timing of this assessment is linked to the treatment effect that is used to justify the NI margin.

Definitions of clinical response are included in the following table. At the DCIV visit, the investigator assessed the clinical response as "cured", "improved", "failure", or "indeterminate" based on comparison to admission signs and symptoms. "Cured" or "improved" response was a favorable clinical response and "failure" was an unfavorable clinical response at the DCIV visit.

Table 26. Study PN004: Definition of Clinical Response at the DCIV Visit

Clinical Response	Response Definition
Cure	All pretherapy signs and symptoms of the index infection have resolved (or returned to "preinfection status") AND no additional IV antibiotic therapy is required.
Failure	No apparent response to IV study therapy in prestudy signs and symptoms, as documented by persistence or progression of most or all pretherapy signs and symptoms. This apparent lack of response can also include any of the following: a) Death related to the intra-abdominal infection at any time point; OR b) Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively; OR c) Evidence of a postsurgical wound infection; OR d) Use of additional (non-study) antibacterial drug therapy for the baseline or a new intra-abdominal infection
Indeterminate	Study data are not available for evaluation of clinical response for any reasons at the DCIV visit, including: a) Complication related to underlying medical condition; OR b) Patient was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical response; OR c) Extenuating circumstances preclude classification as failure d) Death occurred during the study period and the index infection was clearly noncontributory

Source: Table 3-3 of Study Protocol

Clinical response at the EFU visit was defined similarly. Clinical response at the LFU was evaluated as "sustained cure", "failure", "relapse" or "indeterminate" based on comparison to admission signs and symptoms. A favorable clinical response rating at the LFU visit was "sustained cure". An unfavorable clinical response rating at the LFU visit included "failure" or "relapse."

The global response rating considered several factors, including an assessment of signs and

symptoms, all-cause mortality, requirement for unplanned surgical interventions, use of non-study antibiotics, and clinical instability/worsening during the course of the trial. A favorable global response rating at the GFU visit was "cure," as defined in the table below.

Table 27. Study PN004: Definition of Global Response at the GFU Visit

Clinical Response	Response Definition
Cure	Patient meets all 5 of the following criteria: a) All pretherapy signs and symptoms of the baseline intraabdominal infection have resolved in the patient by the GFU visit; AND b) The patient survived through the GFU visit; AND c) The patient did not have an unplanned surgical procedure or percutaneous drainage procedure related to the baseline (or an emergent) intraabdominal infection at any time through the GFU visit; AND d) The patient did not receive any antibacterial drug therapy (e.g., rescue antibacterial drug therapy) to treat the baseline (or an emergent) intra-abdominal infection at any time after IV study therapy was initiated and through the GFU visit; AND e) The patient did not suffer any other event related to the baseline (or an emergent) intra-abdominal infection which resulted in clinical instability or clinical worsening of the patient through the GFU visit.
Failure	Patient does not fulfill 1 or more of the 5 criteria outlined above for "cure"
Indeterminate	Study data are not available for evaluation of global response for any reasons at the GFU visit, including: a) Complication related to underlying medical condition b) Patient was withdrawn for any reason before sufficient data had been obtained to permit evaluation of global response c) Extenuating circumstances preclude classification as "cure" or "failure"

Source: Table 3-6 of Study Protocol

Key Inclusion and Exclusion Criteria

Inclusion criteria

1. Subject was ≥18 years of age on the day of signing informed consent (Visit 1).

   NOTE: Adults were the intended study population for this protocol. Subjects under the age of legal consent were excluded from participation in this study.

2. Sexually active females of childbearing potential with a negative urine pregnancy test were eligible for enrollment; however, this must have been followed up with a confirmed negative serum pregnancy test within 48 hours following the screening

visit. A female who was of reproductive potential agreed to remain abstinent or use (or have their partner use) a medically acceptable effective method of birth control for 1 month after study completion.

3. Subject had a clinically suspected and/or bacteriologically documented cIAI that required hospitalization and treatment with IV antibacterial therapy. Subjects were to be enrolled intraoperatively or postoperatively on the basis of operative findings OR subjects may have been enrolled preoperatively on the basis of compelling preoperative clinical findings, as described below:

a) Intraoperative/Postoperative Enrollment

Subjects may have been enrolled intraoperatively or postoperatively upon visual confirmation (e.g., presence of pus within the abdominal cavity) of an IAI. Surgical intervention included open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery. The initial surgical intervention should have been adequate, as defined in the 2010 Infectious Disease Society of America/Surgical Infections Society guidelines for the management of cIAI.

Diagnoses considered eligible for this study were those in which there was evidence of intraperitoneal infection:

1) Cholecystitis (including gangrenous) with rupture, perforation, or progression of the infection beyond the gallbladder wall
2) Diverticular abscess
3) Appendiceal perforation and periappendiceal abscess
4) Acute gastric and duodenal perforations, only if operated on >24 hours after perforation occurs
5) Traumatic perforation of the intestines, only if operated on >12 hours after perforation occurs
6) Peritonitis due to perforated viscus, surgical intervention, or other focus of infection. Spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites are not eligible.
7) Intra-abdominal abscess (including of liver and spleen)

NOTE: Infections limited to the hollow viscus, such as simple cholecystitis and simple appendicitis, were not eligible. Ischemic bowel disease without perforation was also not eligible. Additionally, acute suppurative cholangitis and acute necrotizing pancreatitis were not eligible because the primary intervention in the former is Endoscopic Retrograde Cholangiopancreatography, and for the latter a single operative intervention was not definitive treatment.

NOTE: Postoperative (or intraoperative) enrollment of subjects was encouraged. If, however, preoperative data were available that strongly suggested an appropriate diagnosis for entry (e.g., intraperitoneal abscess on computed tomography [CT] scan), then these subjects could have been enrolled preoperatively.

NOTE: Specimens from the surgical intervention must have been sent for aerobic and anaerobic culture and susceptibility testing. Only subjects with an intra-operative culture positive for the presence of at least 1 Gram-negative enteric(s) and/or anaerobic pathogen(s) commonly isolated in IAI were considered microbiologically evaluable.

NOTE: Details of interventional operative procedures were recorded in the appropriate eCRF, and an anonymized copy of the operative note and/or interventional radiological report was also collected with the initial and any subsequent intervention. Within the eCRF, it was necessary to record the anatomic site of infection, the etiologic mechanism, and whether there was presence of a single abscess, multiple abscesses, and/or peritonitis.

b) For Preoperative Enrollment

The following clinical criteria needed to be met at screening, and the subject's infection needed to be confirmed by a surgical intervention within 24 hours of entry:

1) Evidence of a systemic inflammatory response, with at least 1 of the following:
    a) Fever (defined as ≥38.0°C [≥100.4°F] orally OR an oral equivalent [≥38.5°C (≥101.3°F) by tympanic or rectal measurement])
    b) Elevated WBC (≥10,500/mm^3)
    c) Drop in blood pressure (systolic blood pressure must be <90 mm Hg without the need for pressor support)
    d) Increased pulse and respiratory rates
    e) Hypoxemia
    f) Altered mental status

AND

2) At least 1 physical finding consistent with IAI, such as:
    a) Abdominal pain and/or tenderness
    b) Localized or diffuse abdominal wall rigidity
    c) Abdominal mass
    d) Ileus

AND

3) Supportive radiologic findings in abdomen, such as intraperitoneal abscess, detected on an abdominal CT scan

AND

4) Requirement for surgical intervention, including open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery.

   NOTE: Specimens from the surgical intervention, once performed, must have been sent for aerobic and anaerobic culture and susceptibility testing. Only subjects with an intraoperative culture positive for the presence of at least 1 Gram-negative enteric(s) and/or anaerobic pathogen(s) commonly isolated in IAI were considered microbiologically evaluable.

Exclusion Criteria

1. Subject had an infection which should have been managed by Staged Abdominal Repair or open abdomen technique.

2. Subject with an Acute Physiology and Chronic Health Evaluation (APACHE) II score >30 at screening.

3. Subject received any amount of effective antibiotic therapy (defined as therapy that was known to be active against the identified pathogen) after obtaining the culture for admission to this study (admission culture) and prior to the administration of the first dose of IV study therapy.

4. Subject had an infection which had been treated with >24 hours of systemic antibacterial therapy which was known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to consideration for entry into the study (e.g., >3 doses every 8 hour [q8h] of antibacterial drugs before enrollment).

   NOTE: Subjects on prophylactic antibacterial therapy were enrolled only if their admission culture was confirmed to be positive for at least 1 Gram-negative enteric(s) and/or anaerobic pathogen(s) commonly isolated in IAI.

   NOTE: If a subject had received >24 hours of systemic antimicrobial therapy, there needed to be clear evidence that the subject had failed this regimen or developed the cIAI while on the previous antibiotic regimen. Such evidence included new or continued fever or persistence or worsening of symptoms related to the index infection and persistent positive cultures and persistent laboratory or radiographic changes (if previously present). These measures were confirmed prior to study entry.

5. Subject had a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to carbapenem antibiotics, any cephalosporins, penicillins, or other β-lactam agents.

   NOTE: Subjects with history of mild rash to penicillins or other β-lactams could have been enrolled and closely monitored.

6. Subject had a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to other β-lactamase inhibitors (e.g., tazobactam, sulbactam, clavulanic acid).

   NOTE: Subjects with a history of mild rash to other β-lactamase inhibitors could have been enrolled and closely monitored.

7. Subject had a history of a seizure disorder (requiring ongoing treatment with anti-convulsive therapy or prior treatment with anti-convulsive therapy in the last 3 years).

8. Subject was being treated with valproic acid or had used valproic acid in the 2 weeks prior to screening.

9. Subject had a rapidly progressive or terminal illness (unlikely to survive the approximately 6- to 8-week study period).

10. Subject was pregnant or expecting to conceive, was breastfeeding, or planned to breast feed within 1 month of completion of the study.

11. Subject in whom a response to IV study therapy (IMI/REL or IMI/REL plus placebo) within the timeframe of treatment specified in this protocol was considered unlikely.

12. Subject had a concurrent infection that would have interfered with evaluation of response to the study antibiotics (IMI/REL or IMI/REL plus placebo).

13. Subject had a need for concomitant systemic antimicrobial agents in addition to those designated in the various study treatment groups.

    NOTE: Use of IV vancomycin to treat confirmed or suspected methicillin-resistant Staphylococcus aureus (MRSA) infection or use of linezolid to treat confirmed or suspected MRSA or vancomycin-resistant *Enterococcus* spp. (VRE) infection was allowed.

14. Subject had a cIAI due to a confirmed fungal pathogen.

NOTE: Use of antifungal therapy for treatment of mucocutaneous infections (e.g., vaginal candidiasis or onychomycosis) was allowed.

15. Subject was receiving immunosuppressive therapy, including use of high-dose corticosteroids (i.e., ≥40 mg prednisone or prednisone equivalent per day).

    NOTE: Prior short-term use (≤5 days) of steroid therapy in the 30 days prior to study entry was allowed.

16. Subject was a prior recipient of a renal transplantation.

17. Subject had estimated or actual creatinine clearance of <50 mL/minute.

18. The subject had any of the following laboratory abnormalities at the time of screening:
    - Alanine aminotransferase (ALT) values ≥3 times the Upper Limit of Normal (ULN)
    - Aspartate aminotransferase (AST) values ≥3 times ULN
    - ALT or AST ≥2 times ULN accompanied by total bilirubin >ULN
    - Total bilirubin value ≥2 times ULN

    NOTE: Subjects with acute hepatic failure or acute decompensation of chronic hepatic failure were also excluded.

Statistical Analysis Plan

Analysis Populations

Microbiological Intention-to-Treat Population (MITT): The MITT population included those subjects who met both of the following two conditions:

1. The subject received at least one dose of IV study therapy;

2. The subject's pre-study/post-operative culture grew at least 1 Gram-negative enteric(s) and/or anaerobic pathogen(s) commonly isolated in IAI.

The Applicant used this population as a supportive analysis for the primary efficacy endpoint. For an NI trial, the cIAI guidance recommends the microbiological ITT (all patients randomized to treatment who have a baseline bacterial pathogen known to cause cIAI) as the primary analysis population. Additionally, for an NI assessment, we have considered susceptibility to the control in the definition of the MITT population as discussed in the results section below. Note that showing NI to a control drug to which a patient's infecting organism is resistant does not provide a scientifically sound means to assess efficacy.

Microbiologically Evaluable (ME) Population: The ME population excluded subjects due to

important deviations from the protocol that may have substantially affected the results of the primary efficacy endpoint. Potential violations that may have resulted in the exclusion of a subject from the ME population included the following:

1. The subject failed to meet the protocol definition of cIAI;

2. The subject's pre-study/post-operative culture from the site of infection failed to grow at least 1 Gram-negative enteric(s) and/or anaerobic pathogen(s) commonly isolated in IAI (note: subjects who failed to grow a single Gram-negative enteric and/or anaerobic pathogen from the site of infection were excluded from the ME population; that is, subjects with only Gram-positive pathogens identified were excluded, as well as those that did not have any organisms grow);

3. The subject had significant violations of inclusion/exclusion criteria that could have impacted the efficacy assessment (e.g., receipt of previous or concurrent systemic antibacterial therapy beyond those allowed per protocol);

4. The subject received less than 96 hours of IV study therapy (16 infusions if q6h dosing or 12 infusions if q8h dosing).

Additionally, subjects with indeterminate results were excluded from the analysis of the ME population. The ME population is used by the Applicant for the primary efficacy analysis. We do not agree with the use of this population for the primary analysis due to the multiple exclusions based on post-randomization information, such as the duration of treatment, which may be related to treatment.

Analysis Methods

Sample Size Calculation: The 117 patients per group was based on a 90% clinical response rate for the control group, a microbiological evaluability rate of 60-65%, an 80% statistical power, a 1-sided type I error rate of 0.025, and a 15% NI margin.

Primary Efficacy Analysis: The Applicant's primary endpoint for this study was the proportion of subjects who achieved a favorable clinical response at DCIV in the ME population. A sensitivity analysis using the MITT population was also performed by the Applicant for the primary endpoint. We will assess the trial using the favorable global response at the GFU visit in the MITT population. This was defined as an exploratory endpoint for the trial. Additionally, in order for an NI assessment to be interpretable, it is necessary that the control drug be effective. For this reason, for NI testing we will consider results in the MITT population excluding subjects with infections due to organisms that are resistant to the control.

Any subject who was missing an evaluation for a specific endpoint (clinical or microbiological response) at any particular visit was generally considered as being "indeterminate" for that endpoint and excluded in the ME population. Patients with a clinical response rating of

"indeterminate" were considered as having an unfavorable clinical response in the MITT population.

NI was tested using a two-sided 95% CI for the between-treatment difference with a 15% NI margin. If NI for either REL dose group was established, a subsequent superiority over the control group would be tested. A closed testing procedure was pre-specified and used to control the type I error rate over multiple treatment comparisons (REL 250 mg vs control, followed by 125 mg vs control).

Reviewers' comment: As noted with the cUTI trial, the Agency had noted the scientific issues with interpreting this trial and had recommended modifications to the trial design. The Applicant preferred to retain their proposal. As designed, this ~~in~~ is not an adequate and well-controlled trial and is being evaluated for descriptive purposes only.

Study Results

Protocol Amendments

There were 2 protocol amendments and 3 protocol clarification letters. The amendments were about removal of the Future Biomedical Research information and procedures in Brazil. These amendments were not to influence the efficacy evaluations.

Compliance with Good Clinical Practices

This study was performed in compliance with Good Clinical Practices.

Financial Disclosure

There was no financial interest to disclose.

Patient Disposition

The study was conducted between November 2012 to August 2014, with subjects enrolled at 45 centers in 20 countries (Argentina, Brazil, Bulgaria, Colombia, Estonia, Germany, Greece, Latvia, Lithuania, Mexico, Peru, Poland, Portugal, Romania, Russia, South Africa, China [Taiwan], Turkey, Ukraine, and United States). The following table shows patient disposition. Of the 351 subjects randomized from 45 centers, 347 were treated with at least 1 dose of IV study therapy. The majority of subjects (94%) completed study medication; 96% completed study. Two subjects were randomized to the placebo group but were treated with REL 125 mg. They were included in the planned group. Approximately 79% of the subjects were included in the MITT population and the main reason for exclusion from this population was baseline culture not meeting protocol-specified requirement. A few MITT subjects were excluded from the ME population at DCIV for inadequate duration of IV study therapy, incorrect IV study therapy, and indeterminate response.

Table 28. Study PN004: Study Disposition

	IMI/REL 250 mg n (%)	IMI/REL 125 mg n (%)	IMI/ Placebo n (%)	Total n (%)
Randomized	118	116	117	351
Randomized but not treated	1 (0.8)	2 (1.7)	1 (0.9)	4 (1.1)
Treated with any study therapy	117 (99.2)	114 (98.3)	116 (99.2)	347 (98.9)
Completed study medication	112 (94.9)	107 (92.2)	111 (94.9)	330 (94.0)
Discontinued study medication	5 (4.2)	7 (6.0)	5 (4.3)	17 (4.8)
Adverse event	1 (0.8)	4 (3.4)	3 (2.6)	8 (2.3)
Death	0	1 (0.9)	0	1 (0.3)
Lack of efficacy	0	0	1 (0.9)	1 (0.3)
Loss to follow-up	0	0	1 (0.9)	1 (0.3)
Physician decision	0	2 (1.7)	0	2 (0.6)
Protocol violation	2 (1.7)	0	0	2 (0.6)
Technical problems	1 (0.8)	0	0	1 (0.3)
Withdrawal by subject	1 (0.8)	0	0	1 (0.3)
Completed study	114 (96.6)	109 (94.0)	114 (97.4)	337 (96.0)
Discontinuation from study	4 (3.4)	7 (6.0)	3 (2.6)	14 (4.0)
Adverse event	0	2 (1.7)	0	2 (0.6)
Death	0	1 (0.9)	0	1 (0.3)
Loss to follow-up	0	1 (0.9)	2 (1.7)	3 (0.9)
Progressive disease	0	1 (0.9)	0	1 (0.3)
Protocol violation	3 (2.5)	1 (0.9)	0	4 (1.1)
Technical problems	1 (0.8)	0 (0.0)	0	1 (0.3)
Withdrawal by subject	0	1 (0.9)	1 (0.9)	2 (0.6)
Microbiological ITT (MITT)[1]	89 (75.4)	96 (82.8)	92 (78.6)	277 (78.9)
Subjects excluded from MITT	29 (24.6)	20 (17.2)	25 (21.4)	74 (21.1)
Baseline culture does not meet protocol-specified requirement	28 (23.7)	18 (15.5)	24 (20.5)	70 (19.9)
Received less than 1 dose of IV study therapy	1 (0.8)	2 (1.7)	1 (0.9)	4 (1.1)
Microbiological evaluable (ME) Population at DCIV*	81 (68.6)	86 (74.1)	83 (70.9)	250 (71.2)
MITT subjects excluded from ME at DCIV	8 (6.8)	10 (8.6)	9 (7.7)	27 (7.7)
Inadequate duration of IV study therapy	3 (2.5)	6 (5.2)	2 (1.7)	11 (3.1)
Incorrect IV study therapy	1 (0.8)	0	2 (1.7)	3 (0.9)
Prior or concomitant antimicrobials violation	2 (1.7)	2 (1.7)	2 (1.7)	6 (1.7)
Other (study drug outside of stability)	0	1 (0.9)	1 (0.9)	2 (0.6)
Subjects with indeterminate response at DCIV	2 (1.7)	1 (0.9)	2 (1.7)	5 (1.4)

Note: Percentages were based on number of subjects randomized.
*The numbers of subjects in the ME population for the analysis of EFU were 79, 86, and 81 and for the analysis of LFU were 79, 85, and 79, for the three treatment groups. The differences in sample size were due to different numbers of subjects with indeterminate results at EFU and LFU.
1 An additional 15, 9 and 11 subjects with resistance to the control (IMI) were excluded from the MITT population from the REL 250- mg, 125-mg and control groups for NI testing.

Timing of visits in the MITT population is shown in the following table. The GFU visit occurred around 30 days for all three arms.

Table 29. Study PN004: Timing of Visits in Days from the First Treatment in the MITT Population

Visit		IMI/REL 250 mg N=89 n (%)	IMI/REL 125 mg N=96 n (%)	IMI/Placebo N=92 n (%)	Total N=277 n (%)
DCIV	N (%)	87 (97.8)	92 (95.8)	91 (98.9)	270 (97.5)
	Mean	6.2	5.9	6.2	6.1
	SD	2.3	1.9	2.1	2.1
	Median	6	5	6	6
	Range	2, 14	2, 14	2, 14	2, 14
EFU	N (%)	86 (96.6)	91 (94.8)	90 (97.8)	267 (96.4)
	Mean	12.9	12.5	12.7	12.7
	SD	2.9	2.7	2.6	2.7
	Median	13	12	13	13
	Range	9,23	8,21	8,21	8,23
GFU	N (%)	87 (97.8)	91 (94.8)	90 (97.8)	268 (96.8)
	Mean	30.9	30.8	31	30.9
	SD	2.7	2.5	2.5	2.6
	Median	30	30	31	30
	Range	27,39	27,36	25,39	25,39
LFU	N (%)	64 (71.9)	64 (66.7)	63 (68.5)	191(69.0)
	Mean	40.4	39.8	39.9	40
	SD	4.3	6.1	4	4.8
	Median	40	38.5	40	39
	Range	32,53	33,77	34,50	32,77

Protocol Violations/Deviations

Twenty-five subjects (7.1%) had important protocol deviations as described in the study report. The most common ones were related to inclusion/exclusion criteria and study drug administration. Three subjects were unblinded prematurely, all from the 250-mg group. The unblinding occurred after the subjects completed the study. No data on protocol violations/deviations were provided in the submission.

Demographic Characteristics

The following table shows the demographic characteristics in the trial. There was a slightly

higher proportion of males in the 250-mg REL group. There were no concerning differences between other demographic characteristics in the table.

Table 30. Study PN004: Demographic Characteristics in the MITT Population

	IMI/REL 250 mg N=89	IMI/REL 125 mg N=96	IMI/Placebo N=92	Total N=277
Sex, n(%)				
Male	54 (60.7)	47 (49.0)	52 (56.5)	153 (55.2)
Female	35 (39.3)	49 (51.0)	40 (43.5)	124 (44.8)
Race, n(%)				
Asian	2 (2.2)	4 (4.2)	5 (5.4)	11 (4.0)
Black or African American	2 (2.2)	3 (3.1)	0	5 (1.8)
Multi-racial	3 (3.4)	3 (3.1)	0	6 (2.2)
White	82 (92.1)	86 (89.6)	87 (94.6)	255 (92.1)
Age (years)				
Mean (SD)	47.9 (19.0)	50.1 (17.0)	48.9 (18.1)	49.0 (18.0)
Median	50.0	52.0	47.5	50.0
Range	18.0, 85.0	18.0, 84.0	18.0, 88.0	18.0, 88.0
Age (years), n(%)				
18 to 40	31 (34.8)	26 (27.1)	31 (33.7)	88 (31.8)
41 to 64	38 (42.7)	45 (46.9)	43 (46.7)	126 (45.5)
65 to 74	14 (15.7)	18 (18.8)	7 (7.6)	39 (14.1)
≥75	6 (6.7)	7 (7.3)	11 (12.0)	24 (8.7)
Weight, n(%)				
<70 kg	26 (29.2)	33 (34.4)	29 (31.5)	88 (31.8)
≥70 kg	61 (68.5)	63 (65.6)	59 (64.1)	183 (66.1)
Missing	2 (2.2)	0	4 (4.3)	6 (2.2)
Region, n(%)				
Asia, Pacific	2 (2.2)	4 (4.2)	3 (3.3)	9 (3.2)
Europe	75 (84.3)	78 (81.3)	80 (87.0)	233 (84.1)
South America	6 (6.7)	9 (9.4)	1 (1.1)	16 (5.8)
US/Canada	6 (6.7)	5 (5.2)	8 (8.7)	19 (6.9)

Reviewer comment: The demographic characteristics were generally well-balanced between the different treatment groups and appropriate for the indication with the exception of racial and geographic diversity. The vast majority of patients were white and from Europe, which is not representative of the target population in the United States. There were very few subjects from other racial or ethnic groups. Slightly more subjects were male which is consistent with other cIAI trials. Demographic characteristics were similar between the ME and MITT populations.

Other Baseline Characteristics

The following table shows baseline disease characteristics. About half of the subjects had a

primary diagnosis of complicated appendicitis. A higher proportion of subjects had this diagnosis in the 250-mg group. A subgroup analysis by primary diagnosis is provided in the following section. Other baseline characteristics were well balanced across the different groups.

Table 31. Study PN004: Disease Characteristics in the MITT Population

	IMI/REL 250 mg N=89	IMI/REL 125 mg N=96	IMI/Placebo N=92	Total N=277
Primary diagnosis, n (%)				
Complicated appendicitis	48 (53.9)	50 (52.1)	44 (47.8)	142 (51.3)
Complicated cholecystitis	14 (15.7)	17 (17.7)	15 (16.3)	46 (16.6)
Diverticular abscess	5 (5.6)	2 (2.1)	5 (5.4)	12 (4.3)
Intraabdominal abscess	3 (3.4)	3 (3.1)	4 (4.3)	10 (3.6)
Multiple abscesses	2 (2.2)	3 (3.1)	3 (3.3)	8 (2.9)
Perforated hollow viscus	8 (9)	12 (12.5)	12 (13)	32 (11.6)
Peritonitis	3 (3.4)	1 (1)	1 (1.1)	5 (1.8)
Other	6 (6.7)	8 (8.3)	8 (8.7)	22 (7.9)
Bacteremia, n (%)				
Yes	3 (3.4)	5 (5.2)	3 (3.3)	11 (4.0)
No	86 (96.6)	91 (94.8)	89 (96.7)	266 (96.0)
APACHE score, n (%)				
≤15	86 (96.6)	93 (96.9)	88 (95.7)	267 (96.4)
>15	3 (3.4)	3 (3.1)	4 (4.3)	10 (3.6)
Time of enrollment, n (%)				
Pre-operatively	16 (18.0)	17 (17.7)	10 (10.9)	43 (15.5)
Intra-operatively	4 (4.5)	3 (3.1)	3 (3.3)	10 (3.6)
Post-operatively	69 (77.5)	76 (79.2)	79 (85.9)	224 (80.9)

APACHE: Acute Physiology and Chronic Health Evaluation

Baseline pathogens are displayed in the following table. The most common pathogens were *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*.

Table 32. Study PN004: Baseline Pathogens in the MITT Population

	IMI/REL 250 mg N=89	IMI/REL 125 mg N=96	IMI/Placebo N=92	Total N=277
All pathogen isolates	204 (100)	223 (100)	214 (100)	641 (100)
Acinetobacter baumannii complex	2 (1.0)	0	3 (1.4)	5 (0.8)
Bacteroides caccae	2 (1.0)	1 (0.4)	1 (0.5)	4 (0.6)
Bacteroides fragilis	12 (5.9)	8 (3.6)	12 (5.6)	32 (5.0)
Bacteroides fragilis group	0	1 (0.4)	0	1 (0.2)
Bacteroides ovatus	3 (1.5)	6 (2.7)	4 (1.9)	13 (2.0)

Bacteroides stercoris	2 (1.0)	1 (0.4)	2 (0.9)	5 (0.8)
Bacteroides thetaiotaomicron	7 (3.4)	6 (2.7)	8 (3.7)	21 (3.3)
Bacteroides uniformis	1 (0.5)	8 (3.6)	4 (1.9)	13 (2.0)
Bacteroides vulgatus	4 (2.0)	3 (1.3)	5 (2.3)	12 (1.9)
Citrobacter freundii	1 (0.5)	2 (0.9)	1 (0.5)	4 (0.6)
Enterobacter aerogenes	2 (1.0)	0	1 (0.5)	3 (0.5)
Enterobacter cloacae	7 (3.4)	4 (1.8)	4 (1.9)	15 (2.3)
Escherichia coli	60 (29.4)	63 (28.3)	57 (26.6)	180 (28.1)
Fusobacterium nucleatum	1 (0.5)	4 (1.8)	1 (0.5)	6 (0.9)
Klebsiella oxytoca	2 (1.0)	9 (4.0)	3 (1.4)	14 (2.2)
Klebsiella pneumoniae	11 (5.4)	13 (5.8)	12 (5.6)	36 (5.6)
Prevotella melaninogenica	1 (0.5)	4 (1.8)	2 (0.9)	7 (1.1)
Pseudomonas aeruginosa	13 (6.4)	14 (6.3)	13 (6.1)	40 (6.2)
Other	73 (35.8)	76 (34.1)	81 (37.9)	230 (35.9)

*Subjects may have multiple baseline pathogens

The following table shows specific prior anti-infective therapies by medication class. About 35% of the subjects used one or more prior anti-infective therapies. The most commonly used was imidazole derivatives. A smaller proportion of subjects in the 250-mg group had prior anti-infective therapies. The cIAI guidance states that patients who receive up to 24 hours of prior nontrial antibacterial drug therapy should be eligible for enrollment and that, for patients who are enrolled in the trial after the surgical procedure, only one dose of effective antibacterial drug therapy should be administered postoperatively before randomization. This study included subjects who received more than 1 day of prior non-trial antibacterial drugs. This table included 12, 9, and 17 subjects in the three treatment groups, respectively, with more than 1 day use of prior antibacterial drug therapy(s). This was only allowed if the patient failed the prior therapy or developed the cIAI while on prior therapy. The data provided did not allow us to assess if all these patients had failed prior therapies.

Table 33. Study PN004: Prior Antibacterial Therapies by Medication Class in the MITT Population

	IMI/REL 250 mg N=89	**IMI/REL 125 mg N=96**	**IMI/Placebo N=92**	**Total N=277**
Subjects with one or more prior anti-infective therapies	28 (31.5)	30 (31.3)	38 (41.3)	96 (34.7)
Carbapenems	3 (3.4)	3 (3.1)	5 (5.4)	11 (4.0)
Combination of penicillins, including beta-lactamase inhibitors	5 (5.6)	3 (3.1)	5 (5.4)	13 (4.7)
Combination sulfonamides and trimethoprim including derivatives	0	1 (1.0)	0	1 (0.4)
Combinations of antibacterials	2 (2.2)	1 (1.0)	5 (5.4)	8 (2.9)
Cephalosporins, first-generation	4 (4.5)	3 (3.1)	4 (4.3)	11 (4.0)
Cephalosporins, second-generation	3 (3.4)	8 (8.3)	6 (6.5)	17 (6.1)

Cephalosporins, third-generation	6 (6.7)	8 (8.3)	8 (8.7)	22 (7.9)
Fluoroquinolones	8 (9.0)	2 (2.1)	8 (8.7)	18 (6.5)
Imidazole derivatives	14 (15.7)	12 (12.5)	18 (19.6)	44 (15.9)
Other aminoglycosides	1 (1.1)	4 (4.2)	4 (4.3)	9 (3.2)
Penicillins with extended spectrum	1 (1.1)	3 (3.1)	2 (2.2)	6 (2.2)
Tetracyclines	0	1 (1.0)	0	1 (0.4)

One subject may take more than one therapy.

The following table shows the number (%) of subjects with specific concomitant anti-infective therapies in the MITT population. It was planned to limit the use of non-trial systemic antimicrobials that were active against the identified pathogen while on IV study therapy, except when IV vancomycin was used to treat confirmed or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) infection or linezolid was used to treat confirmed or suspected MRSA or vancomycin-resistant *Enterococcus spp.* (VRE) infection. Approximately 29% of the subjects used concomitant therapies in each treatment group. After assessment of the timing of the concomitant anti-infectives, only three subjects might have had their global response at the GFU impacted by the additional therapy, 1 subject on REL 250 mg and 2 subjects on REL 125 mg. Therefore, it does not appear that this use overly impacted the results.

Table 34. Study PN004: Concomitant Antibacterial Therapies by Medication Class in the MITT Population

	IMI/REL 250 mg N=89	**IMI/REL 125 mg N=96**	**IMI/Placebo N=92**	**Total (N=277)**
Subjects with one or more concomitant anti-infective therapies	26 (29.2)	28 (29.2)	27 (29.3)	81 (29.2)
Cephalosporins, first-generation	4 (4.5)	3 (3.1)	6 (6.5)	13 (4.7)
Cephalosporins, second-generation	2 (2.2)	5 (5.2)	4 (4.3)	11 (4.0)
Cephalosporins, third-generation	2 (2.2)	6 (6.3)	4 (4.3)	12 (4.3)
Combinations of antibacterials	5 (5.6)	3 (3.1)	2 (2.2)	10 (3.6)
Fluoroquinolones	4 (4.5)	4 (4.2)	5 (5.4)	13 (4.7)
Glycopeptide antibacterials	1 (1.1)	1 (1.0)	3 (3.3)	5 (1.8)
Imidazole derivatives	9 (10.1)	14 (14.6)	7 (7.6)	30 (10.8)
Lincosamides	1 (1.1)	0	0	1 (0.4)
Nitrofuran derivatives	0	0	1 (1.1)	1 (0.4)
Other aminoglycosides	2 (2.2)	3 (3.1)	2 (2.2)	7 (2.5)
Other antibacterials	0	0	1 (1.1)	1 (0.4)
Penicillins with extended spectrum	2 (2.2)	1 (1.0)	1 (1.1)	4 (1.4)
Tetracyclines	0	1 (1.0)	1 (1.1)	2 (0.7)
Cephalosporins, first-generation	4 (4.5)	3 (3.1)	6 (6.5)	13 (4.7)

Cephalosporins, second-generation	2 (2.2)	5 (5.2)	4 (4.3)	11 (4.0)
Cephalosporins, third-generation	2 (2.2)	6 (6.3)	4 (4.3)	12 (4.3)
Combinations of antibacterials	5 (5.6)	3 (3.1)	2 (2.2)	10 (3.6)
Fluoroquinolones	4 (4.5)	4 (4.2)	5 (5.4)	13 (4.7)
Glycopeptide antibacterials	1 (1.1)	1 (1.0)	3 (3.3)	5 (1.8)
Imidazole derivatives	9 (10.1)	14 (14.6)	7 (7.6)	30 (10.8)
Lincosamides	1 (1.1)	0	0	1 (0.4)
Nitrofuran derivatives	0	0	1 (1.1)	1 (0.4)
Other aminoglycosides	2 (2.2)	3 (3.1)	2 (2.2)	7 (2.5)
Other antibacterials	0	0	1 (1.1)	1 (0.4)
Penicillins with extended spectrum	2 (2.2)	1 (1.0)	1 (1.1)	4 (1.4)
Tetracyclines	0	1 (1.0)	1 (1.1)	2 (0.7)

A subject may have used more than 1 medication class.

The following table shows a summary of baseline surgical procedure in the MITT population. The 250-mg group had a higher proportion of laparoscopic procedures and a lower proportion of open procedures, compared to the placebo group.

Table 35. Study PN004: Baseline Surgical Procedures in the MITT Population

	IMI/REL 250 mg N=89	**IMI/REL 125 mg N=96**	**IMI/Placebo N=92**	**Total (N=277)**
Procedure Type				
Laparoscopic	27 (30.3)	20 (20.8)	22 (23.9)	69 (24.9)
Not applicable	0	1 (1.0)	0	1 (0.4)
Open	45 (50.6)	68 (70.8)	55 (59.8)	168 (60.6)
Other	1 (1.1)	1 (1.0)	1 (1.1)	3 (1.1)
Percutaneous	16 (18.0)	6 (6.3)	14 (15.2)	36 (13.0)
Irrigation				
Entire abdomen	38 (42.7)	38 (39.6)	45 (48.9)	121 (43.7)
Local	39 (43.8)	47 (49.0)	34 (37.0)	120 (43.3)
Not applicable	10 (11.2)	9 (9.4)	11 (12.0)	30 (10.8)
Other	2 (2.2)	2 (2.1)	2 (2.2)	6 (2.2)
Drains				
Closed suction	1 (1.1)	5 (5.2)	4 (4.3)	10 (3.6)
Not applicable	7 (7.9)	8 (8.3)	9 (9.8)	24 (8.7)
Other	2 (2.2)	7 (7.3)	7 (7.6)	16 (5.8)
Penrose separate site	33 (37.1)	31 (32.3)	32 (34.8)	96 (34.7)
Penrose through wound	20 (22.5)	24 (25.0)	13 (14.1)	57 (20.6)
Percutaneous catheter	26 (29.2)	21 (21.9)	27 (29.3)	74 (26.7)
Wound				
Delayed primary closure	6 (6.7)	6 (6.3)	3 (3.3)	15 (5.4)
Not applicable	9 (10.1)	2 (2.1)	6 (6.5)	17 (6.1)

Other	1 (1.1)	0	0	1 (0.4)
Primary closure	72 (80.9)	85 (88.5)	82 (89.1)	239 (86.3)
Secondary closure	1 (1.1)	3 (3.1)	1 (1.1)	5 (1.8)

Treatment Compliance

Compliance was measured by comparing the number of completed study medication doses (IV) to the number of planned. The mean compliance percentages were higher than 99% in each treatment group. There was no switch to oral therapy.

Efficacy Results

Clinical Response and Global Response in the MITT Population

The following table shows clinical response by visit and global response at the GFU visit. The proportions of favorable clinical response were similar across the three treatment groups and the four time points. The proportion for each group did not reduce much over time. Table 37 reports the breakdown of unfavorable status for the global response endpoint at the GFU visit. For the 250-mg group and the placebo group, these numbers were balanced and there was no concern on the impact of missing data on the efficacy results.

Table 36. Study PN004: Favorable Clinical Response by Visit and Favorable Global Response at GFU in the MITT Population

Visit	IMI/REL 250 mg N=89 n(%)	IMI/REL 125 mg N=96 n(%)	IMI/Placebo N=92 n(%)	Difference (95 CI) (%) REL 250 mg – Placebo REL 125 mg –Placebo
DCIV	80 (89.9)	88 (91.7)	83 (90.2)	-0.3 (-9.6, 8.9) 1.4 (-7.2, 10.3)
EFU	77 (86.5)	85 (88.5)	82 (89.1)	-2.6 (-12.7, 7.2) -0.6 (-10.0, 8.9)
GFU	77 (86.5)	86 (89.6)	78 (84.8)	1.7 (-8.8, 12.3) 4.8 (-5.0, 14.9)
LFU	78 (87.6)	86 (89.6)	79 (85.9)	1.8 (-8.5, 12.0) 3.7 (-5.9, 13.6)

95% CIs of between-treatment differences were based on unconditional asymptotic Miettinen and Nurminen method.

Table 37. Study PN004: Global Response at GFU in the MITT Population

	IMI/REL 250 mg N=89 n(%)	IMI/REL 125 mg N=96 n(%)	IMI/Placebo N=92 n(%)
Favorable	77 (86.5)	86 (89.6)	78 (84.8)
Failure	6 (6.9)	4 (4.4)	8 (8.9)
Indeterminate	4 (4.6)	1 (1.1)	4 (4.4)
Missing value	2 (2.2)	5 (5.2)	2 (2.2)

For an NI assessment of IMI/REL 250 mg, we excluded 26 subjects (15 in the IMI/REL 250 mg

arm and 11 in the IMI arm) whose baseline isolates were resistant to IMI. Detailed below are the number of pathogens resistant to the control by the two treatment arms of interest. Of note, the list denotes the number of pathogens isolated rather than the number of subjects. One subject in the 250-mg group had *Escherichia coli* and *Proteus mirabilis*; in the placebo group, one subject had *Proteus mirabilis* and *Pseudomonas aeruginosa* and one subject had *Morganella morganii* and *Proteus mirabilis*.

IMI/REL 250mg arm (n=16)

- *Acinetobacter baumannii complex* (n=1)
- *Acinetobacter lwoffii* (n=1)
- *Alcaligenes xylosoxidans* (n=1)
- *Escherichia coli* (n=1)
- *Morganella morganii* (n=2)
- *Proteus mirabilis* (n=8)
- *Proteus vulgaris* (n=1)
- *Pseudomonas aeruginosa* (n=1)

IMI/Placebo (n=13)

- *Acinetobacter baumannii complex* (n=2)
- *Morganella morganii* (n=2)
- *Proteus mirabilis* (n=6)
- *Pseudomonas aeruginosa* (n=3)

Reviewer comment: Organisms excluded from the MITT population were resistant to IMI. The majority of these organisms were non-fermenters (Acinetobacter baumanii or Pseudomonas aeruginosa) and Enterobacteriaceae such as Proteus spp. and Morganella spp. Of note, elevated MICs to imipenem are often noted in such Enterobacteriaciae spp.

The 250-mg REL group had an 84% favorable global response proportion compared to 83% on control at the GFU visit with a 95% CI of [-11.1%, 13%]. The lower bound of the 95% CI was -11.1% meaning that the 250-mg REL group could be as much as 11.1% worse than the control group. These results are not able to support the NI of IMI/REL 250-mg group to control based on an NI margin of 10%; however, it meets a 12.5% NI margin considered acceptable for a limited use labeling.

Clinical Response by Visit in the ME Population

The Applicant's primary analysis was clinical response at the DCIV visit in the ME population. The following table shows the clinical response by visit in the ME population. Note subjects with indeterminate status were excluded from the ME population. Therefore, the number of subjects varied over the different visits. Since the lower bound of the 95% CI was greater than the pre-specified NI margin of -15%, the Applicant concluded that both REL group was "at least as effective as" the IMI alone group at the DCIV visit. Subsequent superiority testing was not statistically significant. It is noted that the favorable clinical response proportions for each group did not decrease much over time.

Table 38. Study PN004: Clinical Response by Visit in the ME Population (Applicant's Analysis)

Visit	IMI/REL 250 mg N=89 n (%)	IMI/REL 125 mg N=96 n (%)	IMI/Placebo N=92 n (%)	Difference (95 CI) (%) REL 250 mg – Placebo REL 125 mg –Placebo
DCIV	78/81 (96.3)	85/86 (98.8)	79/83 (95.2)	1.1 (-6.2, 8.6) 3.7 (-2.0, 10.8)
EFU	75/79 (94.9)	81/86 (94.2)	78/81 (96.3)	-1.4 (-9.1, 6.0) -2.1 (-9.7, 5.3)
LFU	74/79 (93.7)	81/85 (95.3)	75/79 (94.9)	-1.3 (-9.6, 6.9) 0.4 (-7.2, 8.2)

Source: Adapted from Table 11-1 of Study Report. 95% CIs of between-treatment differences were based on unconditional asymptotic Miettinen and Nurminen method.

Findings in Special/Subgroup Populations or Additional Analyses Conducted on the Individual Trial

Gender, Race, Age, Weight, Region, and Baseline Disease Characteristics

The following table shows favorable global response by baseline variables in the MITT population. When the sample size was large enough, the three treatment groups had similar proportions of favorable response.

Table 39. Study PN004: Subgroup Analyses of Favorable Global Response in the MITT Population

	IMI/REL 250 mg N=89 n (%)	IMI/REL 125 mg N=96 n (%)	IMI/Placebo N=92 n (%)
Age (years)			
< 65	60/69 (87.0)	67/71 (94.4)	60/69 (87.0)
≥ 65	17/20 (85.0)	19/25 (76.0)	17/20 (85.0)
Sex			
Male	46/54 (85.2)	43/47 (91.5)	41/52 (78.8)
Female	31/35 (88.6)	43/49 (87.8)	37/40 (92.5)
Race			
Asian	1/2 (50.0)	3/4 (75.0)	5/5 (100)
Black or African American	2/2 (100)	2/3 (66.7)	0
Multi-racial	3/3 (100)	3/3 (100)	0
White	74/82 (90.2)	80/86 (93.0)	78/87 (89.7)
Region			
Asia, Pacific	1/2 (50.0)	3/4 (75.0)	3/3 (100)
Europe	68/75 (90.7)	72/78 (92.3)	69/80 (86.3)
South America	5/6 (83.3)	9/9 (100)	1/1 (100)
US/Canada	3/6 (50.0)	2/5 (40.0)	5/8 (62.5)

Weight (kg)			
Missing	1/2 (50.0)	3/4 (75.0)	0
<70	21/26 (80.8)	25/29 (86.2)	29/33 (87.9)
≥70	55/61 (90.2)	50/59 (84.7)	57/63 (90.5)
APACHE score			
≤15	77/86 (89.5)	85/93 (91.4)	80/88 (90.9)
>15	3/3 (100)	3/3 (100)	3/4 (75.0)
Bacteremia			
Yes	74/86 (86.0)	82/91 (90.1)	77/89 (86.5)
No	3/3 (100)	4/5 (80.0)	1/3 (33.3)
Time of enrollment			
Pre-operatively	14/16 (87.5)	16/17 (94.1)	9/10 (90.0)
Intraoperatively	4/4 (100)	3/3 (100)	3/3 (100)
Post-operatively	59/69 (85.5)	67/76 (88.2)	66/79 (83.5)
Type of surgical intervention			
Laparoscopic	25/27 (92.6)	19/20 (95.0)	19/22 (86.4)
Not Applicable	0	1/1 (100)	0
Open	38/45 (84.4)	61/68 (89.7)	47/55 (85.5)
Other	1/1 (100)	1/1 (100)	1/1 (100)
Percutaneous	13/16 (81.3)	4/6 (66.7)	11/14 (78.6)
Resistance to imipenem			
Yes	15/15 (100)	9/10 (90.0)	11/11 (100)
No†	62/74 (83.8)	77/86 (89.5)	67/81 (82.7)
Primary diagnosis			
Complicated appendicitis	44/48 (91.7)	45/50 (90.0)	41/44 (93.2)
Complicated cholecystitis	14/14 (100)	16/17 (94.1)	14/15 (93.3)
Diverticular abscess	3/5 (60.0)	2/2 (100)	3/5 (60.0)
Intra-abdominal abscess	1/3 (33.3)	3/3 (100)	3/4 (75.0)
Multiple abscesses	1/2 (50.0)	3/3 (100)	3/3 (100)
Other	5/5 (100)	8/8 (100)	6/6 (100)
Perforated hollow viscus	8/8 (100)	8/12 (66.7)	8/12 (66.7)
Peritonitis	1/3 (33.3)	1/1 (100)	0
Prior anti-infective use			
Yes	18/28 (64.3)	25/30 (83.3)	27/38 (71.1)
No	59/61 (96.7)	61/66 (92.4)	51/54 (94.4)
All baseline pathogens	179/204 (87.7)	202/223 (90.6)	179/214 (83.6)
Acinetobacter baumannii complex	2/2 (100)	0	3/3 (100)
Bacteroides caccae	2/2 (100)	1/1 (100)	1/1 (100)
Bacteroides fragilis	11/12 (91.7)	8/8 (100)	10/12 (83.3)
Bacteroides fragilis group	0	1/1 (100)	0
Bacteroides ovatus	2/3 (66.7)	6/6 (100)	4/4 (100)
Bacteroides stercoris	2/2 (100)	1/1 (100)	2/2 (100)
Bacteroides thetaiotaomicron	5/7 (71.4)	6/6 (100)	6/8 (75.0)
Bacteroides uniformis	1/1 (100)	8/8 (100)	4/4 (100)

Bacteroides vulgatus	3/4 (75.0)	3/3 (100)	3/5 (60.0)
Citrobacter freundii	1/1 (100)	2/2 (100)	0/1 (0)
Enterobacter aerogenes	2/2 (100)	0	1/1 (100)
Enterobacter cloacae	7/7 (100)	4/4 (100)	4/4(100)
Escherichia coli	53/60 (88.3)	56/63 (88.9)	45/57 (78.9)
Fusobacterium nucleatum	1/1 (100)	3/4 (75.0)	1/1 (100)
Klebsiella oxytoca	2/2 (100)	8/9 (88.9)	2/3 (66.7)
Klebsiella pneumoniae	9/11 (81.8)	12/13 (92.3)	10/12 (83.3)
Prevotella melaninogenica	1/1 (100)	4/4 (100)	1/2 (50.0)
Pseudomonas aeruginosa	11/13 (84.6)	14/14 (100)	10/13 (76.9)

*One subject may have more than one baseline pathogen. †The difference between the REL 250-mg group and placebo group in the imipenem-susceptible subjects and its 95% CI were 1.1% [-11.1%, 13.0%], based on unconditional asymptotic Miettinen and Nurminen method.

Conclusion on Efficacy

As with study PN003, this trial was not designed to provide evidence of the added contribution of REL 250 mg to IMI or to provide an NI assessment of IMI/REL 250 mg to IMI alone using the appropriate analysis population and endpoint. If the study is assessed posthoc using the appropriate analysis population (MITT) and endpoint (clinical response at GFU), the trial meets an acceptable NI margin for a limited use indication of 12.5%. Given the limitations in the design of this trial, it is difficult to draw conclusions from this posthoc analysis. As with the cUTI trial, the clinical utility of this NI comparison of IMI/REL to IMI is limited and this assessment primarily demonstrates that the addition of REL 250 mg does not reduce the known efficacy of IMI more than what would be considered acceptable for a new treatment.

7.3.3 Study PN013 (Resistant Pathogens)

Trial Objectives

The trial objectives included:

1. To estimate the proportion of subjects with favorable 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 HABP/VABP, (b) clinical response at Day 28 post-randomization for subjects with cIAI, and (c) the composite clinical and microbiological response at the EFU Visit; Day 5 to 9 following the end of therapy (EOT) for subjects with cUTI.

2. To evaluate the safety and tolerability profile of IMI/REL (Treatment Group 1 only).

Trial Design and Endpoints

This was a multicenter, randomized, double-blind, active comparator-controlled trial of the efficacy and safety of IMI/REL versus colistimethate sodium (CMS) + IMI in subjects with imipenem-resistant bacterial infections, including HABP/VABP, cIAI, and cUTI. The study pharmacist was unblinded at a study site for preparing the IV therapy.

Eligible subjects were randomized (2:1) to Treatment Group 1 (IMI/REL + placebo for CMS) or Treatment Group 2 (CMS + IMI) by infection type (HABP/VABP, cIAI, or cUTI). A non-randomized, unblinded/open-label group (Treatment Group 3) was included to enroll eligible subjects to receive IMI/REL.

- Treatment Group 1: IMI/REL (500 mg/250 mg), every 6 hours, IV
- Treatment Group 2: CMS (300 mg) loading dose, followed after 12 hours by maintenance dose, every 12 hours, IMI (500 mg), every 6 hours, IV.
- Treatment Group 3 (open-label): IMI/REL (500 mg/250 mg), every 6 hours, IV

IV study therapy was planned to be administered for a minimum of either 5 (cIAI and cUTI) or 7 (HABP/VABP) days up to a maximum of 21 days. No oral switch was included. For subjects with renal insufficiency, the doses of IMI/REL, IMI, and CMS were adjusted based on the degree of renal function impairment.

Creatinine Clearance (mL/min)	IMI/REL[a]	IMI
≥ 90	500/250 mg q6h	500 mg q6h
< 90 to ≥ 60	400/200 mg q6h	400 mg q6h
< 60 to ≥ 30	300/150 mg q6h	300 mg q6h
< 30 to ≥ 15	200/100 mg q6h	200 mg q6h

[a] IMI/REL is provided as a single vial in a fixed-dose combination; therefore, the dose for each component will be adjusted equally during preparation. For example, a Treatment Group 1 subject who has a creatinine clearance of 50 mL/min should receive a 150 mg q6h dose of REL according to the table. Since the dose is reduced by 50% during preparation, the total mg of IMI would also be reduced by 50%, thus resulting in a 300 mg q6h dose of IMI.

Source: Table 12 of Study Protocol

Study visits included on therapy (OTX, Day 3), EOT, EFU (Days 5 to 9 post-EOT), and Day 28 (after randomization).

Primary Endpoint

The primary endpoint was overall response. Favorable overall response was assessed for each of the 3 infection types. Overall response was 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

Reviewer comment: The endpoints included under the overall clinical response are quite different for each of the three indications.

Definitions of the clinical response at the EFU and Day 28 post-randomization visit are as follows:

Table 40. Study PN013: Definition of Clinical Response

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

[a].A favorable clinical response at EFU or Day 28 post-randomization requires an assessment of "cure" or "sustained cure". To be considered "sustained cure", the clinical response for the prior visit must have been considered "cure". A clinical response of "cure" is only relevant at EFU for subjects with a response of "improved" at EOT.
[b]. Regardless of whether or not the EFU visit is combined with the Day 28 post-randomization visit, the clinical response ratings for all visits should be entered separately in the database.

Source: Adapted from Table 5 of Study Protocol

Subjects with cUTI were evaluated for microbiological response, which included an evaluation for each baseline pathogen (i.e., by-pathogen). Definitions of the by-pathogen microbiological response at the EFU visit are as follows:

Table 41. Study PN013: Definition of Microbiological Response for cUTI Patients at the EFU Visit

Microbiological Response[a,b]	Response Definition
Sustained eradication	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.
Persistence	A urine culture taken at the EFU visit grows a uropathogen (at $\geq 10^4$ CFU/mL) found at study entry.
New Infection	A uropathogen, other than a microorganism found at baseline is present in the urine (at a level $\geq 10^5$ CFU/mL) any time after IV study therapy is finished; OR A pathogen is isolated from a distant (non-urine), sterile after IV study therapy has been completed
Recurrence	A urine grows a uropathogen (at a level $\geq 10^5$ CFU/mL) taken any time after documented eradication.
Indeterminate	a) Follow-up urine culture is not available at the EFU visit due to subject death or withdrawal from study; OR b) Microbiological data are incomplete; OR c) Assessment not possible due to protocol violation; OR d) Any other circumstance which makes it impossible to define the microbiological response; OR e) For Treatment Groups 1 and 2 only, the pathogen does not meet all of the following criteria: • Gram-negative • Resistant to IMI • Susceptible to IMI/REL • Susceptible to colistin; OR f) For Treatment Group 3 only, the pathogen does not meet all of the following criteria: • Gram-negative • Resistant to IMI • Resistant to colistin • Susceptible to IMI/REL

[a]A microbiological response rating will be determined separately for each pathogen isolated at baseline. If a new/emergent pathogen is identified at this visit which was not identified at baseline, the microbiological response rating will be considered a "new infection" for any new/emergent pathogen isolated after initiation of IV study therapy.
[b]A favorable overall microbiological response at EFU visit requires "sustained eradication" of all baseline pathogens.

Source: Adapted from Table 8 of Study Protocol

Microbiological response at Day 3 (OTX) visit and the EOT visit was defined similarly.

Key Secondary Endpoints

The key secondary endpoints for efficacy and safety are as follows:

1. A favorable 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.

Other Secondary Endpoints

1. The proportion of subjects with a favorable clinical response at the OTX, EOT, and EFU Visits.

2. The proportion of subjects with a favorable microbiological response at the OTX, EOT, and EFU Visits.

3. The proportion of subjects with favorable overall response for each infection type.

Inclusion and Exclusion Criteria

Inclusion criteria

Inclusion criteria were separate for Treatment Groups 1 and 2, and Group 3.

Treatment Groups 1 and 2

In order to be eligible for participation in this trial, the subject must:

1. be ≥ 18 years of age.

2. require hospitalization and treatment with IV antibacterial therapy for a new, persistent (defined as inadequate response to current therapy or failure to improve as expected) or progressing (defined as clinically worsening despite treatment) bacterial infection with at least one of the following primary infection types:

- HABP or VABP
- cIAI
- cUTI

Note: Diagnostic criteria, include relevant radiographic, clinical and microbiological evidence.

3. has positive culture data obtained from the primary infection-site specimen collected within 1 week of study entry and at least one of the suspected causative pathogen(s) from that specimen meets all of the following criteria:

   a) has been identified as a gram-negative bacterium, AND
   b) has culture-confirmed imipenem resistance (MIC of isolate is above the imipenem-susceptible breakpoint) based on panels provided by the Sponsor, AND
   c) has culture-confirmed susceptibility to colistin (MIC of isolate is at or below the colistin-susceptible breakpoint) and to IMI/REL (MIC of isolate is at or below the imipenem-susceptible breakpoint) based on panels provided by the Sponsor.

4. Meet one of the following categories:

   a) The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

   b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

   c) The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner from the time of consent through completion of the study by complying with one of the following: (1) practice abstinence from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity.

Treatment Group 3 (Open Label, Nonrandomized)

In order to be eligible for participation in this trial, the subject must meet all the same criteria for randomized Treatment Group 1 and 2 as listed above.

Exclusion Criteria

Treatment Groups 1 and 2

1. has an APACHE II score >30 at screening

2. has an infection in which any of the causative pathogens are any of the following:
   - Imipenem-resistant *Acinetobacter* spp.
   - suspected Class B metallo-beta-lactamase-producing bacteria (including NDM-1, IMP or VIM-containing strains)

3. has a concurrent infection that would interfere with evaluation of response to the study drugs (IMI/REL or CMS + IMI), including any of the following: study drugs (IMI/REL or CMS + IMI), including any of the following:
   - endocarditis
   - osteomyelitis
   - meningitis
   - prosthetic joint infection
   - active pulmonary tuberculosis
   - a disseminated fungal infection

   NOTE: Subjects in whom fungal pathogens are isolated are eligible for participation provided that treatment of the fungus is not planned.

4. has received treatment with any form of systemic colistin for > 24 hours within the 72 hours immediately prior to initiation of study therapy.

5. has HABP/VABP caused by an obstructive process, including lung cancer (or other malignancy metastatic to the lungs resulting in pulmonary obstruction) or other known obstruction.

6. has cUTI which meets any of the following:
   - complete obstruction of any portion of the urinary tract (requiring a permanent indwelling urinary catheter or instrumentation)
   - known ileal loop
   - intractable vesico-ureteral reflux
   - presence of indwelling urinary catheter which cannot be removed at study entry

   NOTE: All indwelling urinary catheters must be removed prior to the start of IV therapy. Unless medically necessary, it is recommended that an indwelling urinary catheter not be reinserted while on IV study therapy

7. has a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to any of the following:

- any carbapenem, cephalosporin, penicillin, or other β-lactam agent
- colistimethate sodium (colistin) or to polymyxin B
- other β-lactamase inhibitors (e.g., tazobactam, sulbactam, clavulanic acid, avibactam)

NOTE: Subjects with a history of mild rash to penicillins or other β-lactams may be enrolled and closely monitored.

8. is a female who is pregnant or is expecting to conceive (or is a male partner of a female who is expecting to conceive), is breastfeeding, or plans to breastfeed prior to completion of the study.

9. has any of the following medical conditions at screening:

   - history of a seizure disorder (requiring ongoing treatment with anti-convulsive therapy or prior treatment with anti-convulsive therapy within the last 3 years)
   - myasthenia gravis
   - porphyria
   - cystic fibrosis
   - granulomatous disease

10. is anticipated to be treated with any of the following medications during the course of study therapy:

    - valproic acid or divalproex sodium (or has used valproic acid or divalproex sodium in the 2 weeks prior to screening)
    - concomitant systemic (IV or oral) antimicrobial agents with known gram-negative bacterial coverage, in addition to those designated in the study treatment groups

    NOTE: Use of IV vancomycin, IV daptomycin, or IV linezolid to treat confirmed or suspected methicillin-resistant *S. aureus* (MRSA) infection or use of IV linezolid or IV daptomycin to treat confirmed or suspected vancomycin-resistant *Enterococcus spp.* (VRE) infection is allowed.

11. has an estimated or actual creatinine clearance of less than 15 mL/min at screening based on the findings of local laboratory values.

12. is currently undergoing hemodialysis.

Treatment Group 3 (Open-Label, Nonrandomized)

The exclusion criteria for Treatment Group 3 are the same as for Treatment Groups 1 and 2 with the exception of a concurrent infection that would interfere with evaluation of response to IMI/REL only, as subjects in the group did not receive CMS + IMI.

Statistical Analysis Plan

Analysis Populations

The populations that were used for the analyses were defined as follows:

- **Microbiological modified intent-to-treat (mMITT) population**: all randomized subjects who received at least 1 dose of each trial drug within a given IV trial treatment regimen, and who had a baseline bacterial pathogen that met inclusion criteria (#3).

- **Per-protocol (PP) population**: subset of the mMITT population who met important diagnostic criteria for entry into the trial, had no significant deviation from the protocol that could impact the assessment of efficacy, and received the minimum duration of IV trial treatment.

Statistical Methods

This trial was for estimation only, with 95% CIs for efficacy endpoints calculated using the Agresti & Coull method. No formal statistical testing was performed.

Protocol Amendments

There were 3 amendments. The changes were about allowing a potential increase in enrollment for any of the three infection type strata; requiring Sponsor's approval of duration of study therapy longer than 21 days; adding a calculation of 90% CIs for between-group differences for the primary efficacy endpoint and key secondary efficacy endpoints across the entire trial population and by specified subgroup, with stratification by infection type where appropriate. There changes were not to affect the efficacy results.

Reviewer's comment: Note that the Division disagreed with the use of 90% CIs to assess possible superiority of the test arm to the control and stated that 95% CIs should be used. Note that superiority was not found in this study using either CI level.

Study Results

Compliance with Good Clinical Practices

This trial was conducted in in conformance with applicable country or local requirements.

Financial Disclosure

There was no financial interest to disclose.

Patient Disposition

This trial was conducted from October 2015 to March 2018, with subjects screened at 17 centers in 12 countries (Brazil, Colombia, Estonia, Germany, Latvia, Lithuania, Mexico, Peru, Romania, Turkey, Ukraine, and United States). The following table shows the patient disposition. A total of 54 subjects were screened and 50 were enrolled. All enrolled subjects were treated and received the treatment as planned. The majority of the subjects completed the study and study medication. There were 5 deaths in total. The following analyses will focus on the two randomized groups, because only 3 subjects were in the non-randomized, open-label group.

Table 42. Study PN013: Study Disposition

	IMI/REL + Placebo for CMS n (%)	CMS + IMI n (%)	IMI/REL n (%)	Total n (%)
Enrolled	31	16	3	50
Randomized	31	16	0	47
Treated	31 (100)	16 (100)	3 (100)	50 (100)
Trial disposition				
Completed	27 (87.1)	11 (68.8)	1 (33.3)	39 (78.0)
Discontinued	4 (12.9)	5 (31.3)	2 (66.7)	11 (22.0)
Adverse event	0	1 (6.3)	1 (33.3)	2 (4.0)
Death	1 (3.2)	3 (18.8)	1 (33.3)	5 (10.0)
Loss to follow-up	1 (3.2)	1 (6.3)	0	2 (4.0)
Physician decision	1 (3.2)	0	0	1 (2.0)
Withdrawal by subject	1 (3.2)	0	0	1 (2.0)
Study medication				
Completed	27 (87.1)	11 (68.8)	1 (33.3)	39 (78.0)
Discontinued	4 (12.9)	5 (31.3)	2 (66.7)	11 (22.0)
Adverse event	0	3 (18.8)	1 (33.3)	4 (8.0)
Death	0	1 (6.3)	1 (33.3)	2 (4.0)
Physician decision	2 (6.5)	1 (6.3)	0	3 (6.0)
Treatment failure	1 (3.2)	0	0	1 (2.0)
Withdrawal by subject	1 (3.2)	0	0	1 (2.0)
Microbiological modified intent-to-treat (mMITT) population	21 (67.7)	10 (62.5)	0	31 (62.0)
Exclusion from mMITT	10 (32.3)	6 (37.5)		
Pathogen from infection-site culture does not meet protocol-specified susceptibility criteria	8 (25.8)	5 (31.3)		
Qualifying culture collected greater than 1 week prior to entry	2 (6.5)	1 (6.3)		

Protocol Violations/Deviations

Overall 33 subjects in the study had protocol deviations. The most common deviations were related to study procedures, compliance of treatment, inclusion/exclusion criteria, and receipt of prohibited medications.

Demographic Characteristics

Demographic and baseline characteristics are included in the following table. Most subjects were younger than 65 years of age. The majority were male and 90% of subjects were white.

Table 43. Study PN013: Demographic and Baseline Characteristics in the mMITT Population

	IMI/REL + Placebo for CMS (N=21)	CMS + IMI (N=10)
Age (years)		
Mean (SD)	53.6 (16.9)	63.3 (11.3)
Median	59.0	60.5
Range	19, 75	49, 80
Age (years), n (%)		
<65	15 (71.4)	5 (50.0)
≥65	6 (28.6)	5 (50.0)
Sex, n (%)		
Male	13 (61.9)	7 (70.0)
Female	8 (38.1)	3 (30.0)
Body weight (kg)		
Mean (SD)	76.4 (19.6)	75.2 (19.6)
Median	75.0	75.6
Range	53.0, 132.3	52.8, 117.0
Race, n (%)		
Multiple	3 (14.3)	0
White	18 (85.7)	10 (100)
Region, n (%)		
Europe	18 (85.7)	8 (80)
North America	0	1 (10)
South America	3 (14.3)	1 (10)
Primary diagnosis, n (%)		
HABP	1 (4.8)	1 (10)
VABP	7 (33.3)	2 (20)
cIAI	2 (9.5)	2 (20)
cUTI with UT abnormalities	5 (23.8)	3 (30)
cUTI, acute pyelonephritis	6 (28.6)	2 (20)
Bacteremia, n (%)		

Yes	1 (4.8)	1 (10)
No	5 (23.8)	2 (20)
Unknown	15 (71.4)	7 (70)
APACHE II score, n (%)		
≤15	14 (66.7)	8 (80)
>15	7 (33.3)	2 (20)
Baseline pathogen, n (%)		
Single pathogen isolated (mono-microbial)	21 (100)	9 (90)
Multiple pathogens isolated (poly-microbial)	0	1 (10)
Creatinine clearance (mL/min), n (%)		
15 to <30	1 (4.8)	1 (10)
30 to <60	3 (14.3)	2 (20)
60 to <90	8 (38.1)	4 (40)
90 or higher	8 (38.1)	3 (30)
Not applicable	1 (4.8)	0
Baseline pathogen		
HABP/VABP	8	3
Pseudomonas aeruginosa	8 (100)	3 (100)
cIAI	2	3
Citrobacter freundii	1 (50)	0
Klebsiella pneumoniae	0	1 (10)
Pseudomonas aeruginosa	1 (50)	2 (100)
cUTI	11	5
Enterobacter cloacae	1 (9.1)	0
Klebsiella oxytoca	0	1 (20)
Klebsiella pneumoniae	3 (27.3)	1 (20)
Pseudomonas aeruginosa	7 (63.6)	3 (60)
All	21	10
Citrobacter freundii	1 (4.8)	0
Enterobacter cloacae	1 (4.8)	0
Klebsiella oxytoca	0	1 (10)
Klebsiella pneumoniae	3 (14.3)	2 (20)
Pseudomonas aeruginosa	16 (76.2)	8 (80)

Other Baseline Characteristics

As seen in the previous table, about half of the subjects had a primary diagnosis of cUTI and 29% of subjects had VABP. Only two subjects had bacteremia at baseline. Most subjects had an

APACHE II score ≤15. Single baseline pathogen was observed in 97% of the subjects. One subject in the placebo group had *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The most common pathogen was *Pseudomonas Aeruginosa.*

Treatment Compliance, Concomitant Medications

Compliance was measured by comparing the number of completed doses to the number of expected doses of IV trial treatment. The compliance percentage was high in both randomized treatment groups. The mean treatment duration was 11.5 days for the two groups.

The following table shows systemic anti-infective use in the mMITT population. About 84% of the subjects took prior antibacterial drugs for systemic use. About two thirds of the subjects took concomitant antibacterial drugs for systemic use. Only a small proportion of subjects used antifungal or antiviral drugs prior or concomitantly.

Table 44. Study PN013: Systemic Antimicrobial Therapy in the mMITT Population

	IMI/REL + Placebo for CMS N=21	**CMS + IMI N=10**
Prior use		
Antibacterials	18 (85.7)	8 (80.0)
Antifungals	4 (19.0)	3 (30.0)
Antivirals	1 (4.8)	1 (10.0)
Concomitant use		
Antibacterials	14 (66.7)	7 (70.0)
Antifungals	3 (14.3)	3 (30.0)
Antivirals	2 (9.5)	2 (20.0)

Efficacy Results

The favorable overall response in the mMITT population was the primary endpoint. As the following table shows, favorable overall response proportions were about 70% in both randomized treatment groups. Results are also given by infection type.

Favorable clinical response at Day 28 in the IMI/REL group was higher than the CMS+IMI group and all-cause mortality through Day 28 was lower. However, given the small sample size, the results are highly variable.

Table 45. Study PN013: Efficacy Analysis in the mMITT Population

	IMI/REL + Placebo for CMS N=21 n(%) [95% CI]	**CMS + IMI N=10 n(%) [95% CI]**
Primary analysis[1]		

Favorable overall response	15 (71.4) [49.8, 86.4]	7 (70.0) [39.2, 89.7]
HABP/VABP (N=11): survival through Day 28	7/8 (87.5)	2/3 (66.7)
cIAI (N=4): clinical response at Day 28	0/2 (0)	0/2 (0)
cUTI (N=16): clinical-microbiological response at EFU	8/11 (72.7)	5/5 (100)
Secondary analyses		
Favorable clinical response at Day 28	15 (71.4) [49.8, 86.4]	4 (40.0) [16.7, 68.8]
HABP/VABP	5/8 (62.5)	0/3 (0)
cIAI	0/2 (0)	0/2 (0)
cUTI	10/11 (90.9)	4/5 (80.0)
All-cause mortality through Day 28	2 (9.5) [1.4, 30.1]	3 (30.0) [10.3, 60.8]
HABP/VABP	1 (4.8)	1 (10.0)
cIAI	1 (4.8)	1 (10.0)
cUTI	0	1 (10.0)

95% CIs were based on Agresti & Coull method and not presented for sample size less than 4.
[1] one patient in each arm had missing data for the cIAI stratum and one patient on the IMI/REL arm had missing data for the cUTI stratum. One subject with cUTI and one subject with HABP/VABP in the IML/REL group failed due to relapse. 95% exact CI on the difference in favorable overall response was (-31.6%, 39.4%). 90% exact CI on the difference in favorable overall response was (-30.5%, 32.8%). The adjusted difference and 90% CI based on Miettinen & Nurminen method stratified by infection-site from stratum by the Applicant was -7.3% (-27.5%, 21.4%).

Findings in Special/Subgroup Populations or Additional Analyses Conducted on the Individual Trial

Sex, Age, Body Weight, Region, and Baseline Disease Characteristics

Subgroup analysis results are included in the following table. For most subgroups, when the sample sizes were relatively large, the favorable overall response proportions were comparable, with no outliers noted. In Europe, the favorable clinical response proportion was greater than 75% in both groups. In other regions, the sample size was too small to make a reliable estimate. Prior or concomitant anti-bacterial systemic use appeared not to impact the favorable overall response between the two treatment groups, although the users had a worse response within a treatment group. Subjects with an APACHE score ≤15 in the IMI/REL group had a higher response proportion than that in the CMS+IMI group.

Table 46. Study PN013: Subgroup Analysis of Favorable Overall Response in the mMITT Population

	IMI/REL + Placebo for CMS **N=21** **n (%)**	**CMS + IMI** **N=10** **n (%)**

Sex		
Male	8/13 (61.5)	4/7 (57.1)
Female	7/8 (87.5)	3/3 (100)
Race		
Multiple	1/3 (33.3)	0
White	14/18 (77.8)	7/10 (70.0)
Age (years)		
< 65	10/15 (66.7)	3/5 (60.0)
≥ 65	5/6 (83.3)	4/5 (80.0)
Body weight (kg)		
< 70	5/8 (62.5)	2/4 (50.0)
≥ 70	10/13 (76.9)	5/6 (83.3)
Primary diagnosis		
HABP/VABP	7/8 (87.5)	2/3 (66.7)
cIAI	0/2 (0)	0/2 (0)
cUTI	8/11 (72.7)	5/5 (100)
Region		
Europe	14/18 (77.8)	6/8 (75.0)
North America	0	0/1 (0)
South America	1/3 (33.3)	1/1 (100)
Creatinine clearance (mL/min)		
15 to <30	1/1 (100)	1/1 (100)
30 to <60	3/3 (100)	1/2 (50.0)
60 to <90	5/8 (62.5)	3/4 (75.0)
90	5/8 (62.5)	2/3 (66.7)
Not applicable	1/1 (100)	0
APACHE II score		
≤15	12/14 (85.7)	6/8 (75.0)
>15	3/7 (42.9)	1/2 (50.0)
Prior systemic antibacterial use		
Yes	12/18 (66.7)	5/8 (62.5)
No	3/3 (100)	2/2 (100)
Baseline pathogen		
HABP/VABP	7/8 (87.5)	2/3 (66.7)
Pseudomonas aeruginosa	7/8 (87.5)	2/3 (66.7)
cIAI	0/2	0/3
Citrobacter freundii	0/1	0
Klebsiella pneumoniae	0	0/1
Pseudomonas aeruginosa	0/1	0/2
cUTI	8/11 (72.7)	5/5 (100)
Enterobacter cloacae	1/1 (100)	0
Klebsiella oxytoca	0	1/1 (100)

Klebsiella pneumoniae	1/3 (33.3)	1/1 (100)
Pseudomonas aeruginosa	6/7 (85.7)	3/3 (100)
All	15/21 (71.4)	7/11 (70)
Citrobacter freundii	0/1	0
Enterobacter cloacae	1/1 (100)	0
Klebsiella oxytoca	0	1/1 (100)
Klebsiella pneumoniae	1/3 (33.3)	1/2 (50)
Pseudomonas aeruginosa	13/16 (81.3)	5/8 (62.5)

Conclusion of Efficacy

PN013 was a descriptive study with no pre-specified hypothesis testing and as such provides limited information for an efficacy assessment. The primary intent of this study was to gain some clinical experience in patients with infections at different body sites (HABP/VABP, cUTI, cIAI) due to CRE. In this very small study although the two groups achieved similar favorable proportions in overall response, the results are difficult to interpret for many reasons, including the lack of a finding of superiority in the setting of high rates of prior and concomitant antibacterial drug administration, inclusion of different types of infections, and the definition of the clinical response endpoint. The overall mortality rate in the IMI/REL arm was lower than that in the comparator arm; however, the numbers are too small and the confidenece intervals overlap to a large extent precluding the ability to draw any reliable conclusions. Also, from a microbiologic standpoint, there were very few patients with infections due to CRE; the majority of baseline pathogens were *P. aeruginosa*. Some carbapenem resistance in *P. aeruginosa* are from mechanisms other than carbapenemase production.

While we considered if this study could be interpreted as a historically controlled trial, use of historical controls for these types of patient populations, particularly with infection types at different body sites is problematic. Outcomes are highly variable and even with infections due to organisms that are categorized as resistant to available therapies, outcomes are not uniformly poor. The variability in outcomes seen in the trials is often on the order of the magnitude of treatment effect for antibacterial drugs. Cure rates/outcomes vary significantly between body sites- cUTI vs. HABP/VABP and also in a given body site the outcomes vary between trials. The clinical response of ~70% with IMI-REL is really a mixture of outcomes- mortality (HABP/VABP), clinical success at day 28 (cIAI), clinical success at end of IV (cUTI) and comparing that with historical data is difficult.

7.3.4 Assessment of Efficacy Across Trials

The evidence of efficacy of IMI/REL is based in part on the Agency's previous findings of the efficacy of IMI for the treatment of cUTI and cIAI, limited clinical data from a trial each in cUTI and cIAI and a trial in patients with different types of infections due to CRE, along with data from *in vitro* and animal models of infection in which the activity of imipenem against imipenem-nonsusceptible organisms that produce certain class A and C beta lactamases was restored by relebactam. The two studies, PN003 in cUTI and PN004 in cIAI were not

appropriately designed for hypothesis testing, and trial PN013 in patients with different types of infections due to CRE was a descriptive study with no pre-specified hypothesis testing. While designs other than those recommended in guidance documents can be considered, the design of trials PN003 and PN004 had significant limitations that made it difficult to draw reliable conclusions based on their results.

In the cUTI trial, the combined microbiological and clinical endpoint showed numerically lower success proportions at the DCIV and EFU visits for IMI/REL 250 mg compared to control. The lower proportions at the DCIV visit were driven by the microbiological endpoint while the lower proportions at the EFU visit were seen with both clinical and microbiologic endpoint. In the cIAI trial, the proportions of favorable response at the GFU visit appeared similar between the IMI/REL 250-mg arm and the IMI control arm. However, regardless of the efficacy findings in both trials, the clinical utility of an NI comparison between IMI/REL and IMI is limited.

Study PN013, was designed only for estimation and not for hypothesis testing. Although numerically similar favorable overall clinical response proportions were seen in the IMI/REL and CMS+IMI treatment groups, this trial is difficult to interpret due to its small sample size, primary endpoint definition, and varied patient population.

7.4 Review of Safety

7.4.1 Safety Review Approach

The safety of IMI/REL was evaluated in 10 trials; seven Phase 1 trials evaluated REL administered alone, as a co-infusion with IMI or a fixed dose combination of IMI/REL, two trials, one each in cUTI and cIAI, evaluated two doses of REL as a co-infusion with IMI compared with IMI + Placebo and one double-blind trial PN013 evaluated a fixed dose combination of IMI/REL compared to IMI + Colistin in patients with imipenem-resistant organisms. The safety review primarily focuses on trials PN003, PN004, and PN013. Due to differences in study design and study population between trials PN003 and PN004 and PN013, safety data were reviewed separately. Safety data for the PN003 and PN004 was primarily reviewed using the integrated summary of safety (ISS) database provided by the Applicant, while PN013 was reviewed using a separately provided dataset.

The population used for safety data analysis in the trials was the All Subjects as Treated (ASaT) population and consisted of all subjects who received at least one dose of IV trial treatment. Subjects were included in the treatment group corresponding to the treatment they actually received, which for most subjects was also the treatment group they were randomized to.

Reviewer comment: In PN003 and PN004, there was an option to switch to the higher dose, IMI/REL 250mg treatment arm from initial IV trial treatment if the baseline pathogen was imipenem-nonsusceptible and they were not demonstrating a favorable clinical response to study treatment after at least 72 hours. There were 4 subjects who were switched to the higher dose, IMI/REL 250mg. For the purposes of the safety review, subjects were included in the

treatment group corresponding to the treatment they initially received.

Safety evaluation for the trials consisted of AE monitoring, hematology and chemistry laboratory evaluations, vital sign measurement and Events of Clinical Interest (ECI) defined as:

ECI #1: An elevated aspartate aminotransferase (AST) or alanine transaminase (ALT) value ≥5 X upper limit of normal (ULN) or

ECI#2: An elevated AST or ALT value ≥3 X ULN and an elevated total bilirubin value ≥2 X ULN and, at the same time, an alkaline phosphatase value <2 X ULN.

The duration of follow-up for all AEs, including SAEs, was from the first day of IV trial treatment (Day 1) through 14 days after completion of trial treatment. For Study PN003, this included completion of IV trial treatment as well as any subsequent oral ciprofloxacin treatment. For SAEs only, if the investigator considered the event to be possibly, probably or definitely related to trial treatment, it was also reported as event even if it occurred at any time outside of the 14-day follow period following completion of trial treatment.

Reviewer comment: The definition of the duration of follow-up used by the Applicant was not ideal as it was contingent on the length of treatment. This could result in different durations of follow-up between study arms. It would be preferable if the duration of follow-up were defined based on a specified post-randomization day. The duration of IV therapy in studies PN003 and PN004 was similar in all treatment arms.

For the majority of safety analyses, the two IMI/REL treatment arms, IMI/REL 125mg and IMI/REL 250mg were combined. This was done to allow for a more robust analysis and because there were no major differences seen between the two treatment arms regarding safety, unless specifically noted in the review. For example, all 3 deaths occurring in studies PN003 and PN004 occurred in the IMI/REL 125mg treatment and this is noted and discussed in further detail in the relevant section.

Other noted differences between the IMI/REL 125mg and 250mg arms included the number of cases of C. difficile colitis reported (all 3 cases in the ISS population were reported in the IMI/REL 125mg) and a greater number of SAEs reported in the IMI/REL 125mg arm. These differences were attributed to chance findings as they were not dose-dependent, and all occurred in the lower dose arm. There were no differences noted in overall AEs reported, discontinuations, laboratory and chemistry findings or vital sign measurements.

7.4.2 Review of the Safety Database

Overall Exposure

Overall exposure to IMI/REL is depicted in Table 47. The total number of subjects receiving

IMI/REL at the proposed dose of 500mg/250mg at any duration is 304 subjects (54 in the Phase 1 trials, 216 in studies PN003 and PN004 and 34 in PN013), while those receiving the proposed dose and duration were 269 subjects (19 in the Phase 1 trials, 216 in studies PN003 and PN004, and 34 in PN013). Overall, 673 subjects were exposed to IMI/REL at any dose and duration. An additional 48 subjects received IMI/REL at the appropriate dosing for renal impairment of 250/125mg in a Phase 1 trial.

The total number of subjects receiving the proposed marketed dose of IMI/REL 500mg/250mg for at least 96 hours per the reviewer's analysis was 269 subjects, as opposed to 299 subjects cited in the NDA. In response to an information request, the Applicant noted that the discrepancies in exposure duration are due to differences in the calculation of exposure duration based on the individual study dosing frequency schedule. In PN013 duration of exposure was calculated based on calendar days as study drug dosing was every 6 hours. Calculation of duration in the studies PN003 and PN004 was based on the number of doses received and the frequency at which the doses were administered (formula for calculation of duration (days): number of doses x 6/24). Due to this calculation method, subject's creatinine clearance could affect the frequency of administration. Therefore, subjects who received the expected number of doses over 4 days (i.e., 16 doses for subjects dosed every 6 hours or 12 doses for subjects dosed every 8 hours) were counted as receiving a treatment duration of 4 days, even if the actual time between their first and last dose was <96 hours.

Reviewer Comment: The Applicant's explanation for the discrepancies in the safety database was found satisfactory.

Table 47. Safety Database for Imipenem/Relebactam Development Program

Trial	Indication	IMI 500 mg/REL 250mg (n=273)	IMI 500 mg /REL 125mg (n=261)	IMI 250 mg /REL 125mg (n=48)	IMI 500 mg /REL any dose[1] (n=60)	IMI 500mg + CMS (n=16)	IMI 500 mg/REL 250mg+ Placebo to CMS (n=31)	IMI 500mg + Placebo (n=263)	Placebo or Relebactam 1150mg or Moxifloxacin 500mg (n=39)	Total (n= 959)
cUTI and cIAI Trials										
PN003	cUTI	99	99	-	-	-	-	100		298
PN004	cIAI	117	116	-	-	-	-	114		347
cIAI, cUTI, and HABP/VABP Trial										
PN013	cIAI, cUTI, HABP/VABP	3	-	-	-	16	31	-	-	50
Phase 1 Trials										
P001	Safety, tolerability and PK in HV	7	12	-	44	-	-	43		106

P007[2]	Intrapulmonary PK in HV	17	-	-	-	-	-	-		17
P002	Safety, Tolerability and PK in Healthy Elderly and Young Female Volunteers	-	18	-	-	-	-	6		24
P005	PK in Subjects with renal impairment	-	-	48	-	-	-	-		48
P012[3]	PK in Healthy Japanese Volunteers	16	16	-	16	-	-	-	3	19
P019[4]	Effect of Probenecid on PK in HV	14	-	-	-	-	-	-	-	14
P009[5]	QTc in HV	-	-	-	-	-	-	-	36	36

Source: Clinical Reviewer's Analysis

[1]Any dose of IMI/REL apart from 500/250mg or 500/125mg.

[2]Only five doses of IMI 500 mg /REL 250mg administered.

[3]Only 12 patients received proposed duration, remaining 4 only received single doses. Patients may have received more than one dosing regimen, total does not reflect sum of all columns.

[4]Single doses only.

[5]Relebactam 1150mg, Moxifloxacin 500mg or Placebo used in this single-dose, double-blind, randomized, placebo and positive controlled, 3-period, balanced crossover trial

Reviewer comment: Due to the crossover design of some of the Phase 1 trials, some subjects received more than one dosing regimen.

Table 48. Subjects Who Received ≥ 4 days of Imipenem /Relebactam ≥250mg in the Imipenem/Relebactam Development Program[1]

Trial Number	Trial Phase	Number of Subjects
PN001	1	48
PN002	1	0
PN005	1	0
PN007	1	0
PN009	1	0
PN012	1	11
PN019	1	0
PN003	2	97
PN004	2	112
PN013	3	31

Total	299
[1] IMI provided together with REL either as separate simultaneous infusions or as a fixed-dose combination.	

*Source: Applicant's response to FDA information request dated 21-Mar-2019

The primary safety database was comprised of subjects in trials PN003 and PN004 and PN013. The Applicant submitted an Integrated Safety Summary (ISS) for studies PN003 and PN004, which was used for the primary safety analysis of these trials.

The cUTI trial included 99 subjects in the IMI/REL 250mg arm, 99 subjects in the IMI/REL 125mg arm and 100 subjects in the IMI/Placebo arm for a total of 298 subjects.

The cIAI trial included 117 subjects in the IMI/REL 250mg arm, 116 subjects in the IMI/REL 125mg arm and 114 subjects in the IMI/Placebo arm for a total of 347 subjects.

Trial PN013 included 31 subjects in the IMI/REL 250mg + Placebo to colistin arm, 16 subjects in the IMI + colistin arm, and 3 subjects in the IMI/REL 250 mg open-label arm for a total of 50 subjects.

The mean duration of IV treatment was similar in the IMI/REL 250 mg (7.9 days), the IMI/REL 125mg (7.8 days) and the IMI/Placebo (8.2 days) arms (Table 49).

Table 49. Intravenous Study Drug Exposure in Studies PN003 and PN004, Safety population

	IMI/REL 250mg N=215 n (%)	IMI/REL 125mg N=216 n (%)	IMI/Placebo N=214 n (%)
IV Study Drug Exposure (in days)			
<5 days	9 (4.2%)	8 (3.7%)	4 (1.9%)
>=5- <7 days	67 (31.2%)	64 (29.6%)	64 (29.9%)
>=7 - <10 days	82 (38.1%)	96 (44.4%)	91 (42.5%)
>=10 days	57 (26.5%)	48 (22.2%)	55 (25.7%)
Mean duration of IV treatment (days) (mean, SD, min-max range)	7.9 (2.8, 2-15)	7.8 (2.8, 2-15)	8.2 (2.7, 2-15)

Source: Clinical Reviewer's Analysis

Relevant characteristics of the safety population:

The demographic characteristics in the pooled analysis of studies PN003 and PN004 were well balanced. There were slightly more women in the IMI/REL 125mg arm (51.6% vs. 48.4%) and more men in the IMI/REL 250mg (57.4% vs 42.6%) and IMI + Placebo arms. The mean age was 52.5 years. Most subjects were over 65 years of age (69%), white (91%) and from Europe (86%)

(Table 50).

In trial PN013, 62% were men. The mean age was 57.9 years. The majority were over age 65 (56%), white (88%) and from Europe (80%), Table 51.

Table 50. Demographic characteristics: Studies PN003 and PN004, Safety Population

Demographic Parameters	IMI/Placebo N=214 n (%)	IMI/REL 125 mg N=215 n (%)	IMI/REL 250 mg N=216 n (%)	Total (N=645) n (%)
Sex				
Female	92 (43.0%)	111 (51.6%)	92 (42.6%)	295 (45.7%)
Male	122 (57.0%)	104 (48.4%	124 (57.4%)	350 (54.3%)
Age				
Mean years (SD)	52.0 (18.7)	52.9 (17.7)	52.5 (18.7)	52.5 (18.3)
Median (years)	54	55	55	55
Min, max (years)	18, 88	18, 88	18, 90	18, 90
Age Group				
< 65 years	150 (70.1%)	147 (68.4%)	149 (69.0%)	446 (69.1%)
≥ 65 years	64 (29.9%)	68 (31.6%)	67 (31.0%)	199 (30.9%)
Race				
American Indian or Alaska Native	0 (0.0%)	3 (1.4%)	2 (0.9%)	5 (0.8%)
Asian	7 (3.3%)	10 (4.7%)	4 (1.9%)	21 (3.3%)
Black or African American	1 (0.5%)	4 (1.9%)	2 (0.9%)	7 (1.1%)
Multi-racial	7 (3.3%)	7 (3.3%)	10 (4.6%)	24 (3.7%)
White	199 (93.0%)	191 (88.8%)	198 (91.7%)	588 (91.2%)
Ethnicity				
Hispanic or Latino	9 (4.2%)	16 (7.4%)	15 (6.9%)	40 (6.5%)
Not Hispanic or Latino	192 (89.7%)	195 (90.7%)	191 (88.4%)	578 (93.5%)
Region				
Africa	2 (0.9%)	5 (2.3%)	4 (1.9%)	11 (1.7%)
Asia Pacific	5 (2.3%)	6 (2.8%)	4 (1.9%)	15 (2.3%)
Europe	190 (88.8%)	182 (84.7%)	184 (85.2%)	556 (86.2%)
North America	9 (4.2%)	11 (5.1%)	9 (4.2%)	29 (4.5%)
South America	8 (3.7%)	11 (5.1%)	15 (6.9%)	34 (5.3%)

Source: Clinical Reviewer's Analysis

Table 51. Demographic characteristics in Study PN013, Safety Population

Demographic Parameters	IMI + CMS N=16 n (%)	IMI/REL 250 mg + Placebo to CMS N=31 n (%)	IMI/REL 250 mg N=3IMI/REL 250 mg N=3 n (%)	Total N=50 n (%)

Sex				
Female	6 (37.5%)	11 (35.5%)	2 (66.7%)	19 (38.0%)
Male	10 (62.5%)	20 (64.5%)	1 (33.3%)	31 (62.0%)
Age				
Mean years (SD)	62.3 (14.9)	56.1 (16.5)	50 (23.1)	57.9 (16.4)
Median (years)	65.5	59	58	59
Min, max (years)	22, 80	19, 77	24, 68	19, 80
Age Group				
< 65 years	7 (43.8%)	19 (61.3%)	2 (66.7%)	28 (56.0%)
≥ 65 years	9 (56.3%)	12 (38.7%)	1 (33.3%)	22 (44.0%)
Race				
American Indian or Alaska Native	0 (0.0%)	1 (3.2%)	0 (0.0%)	1 (2.0%)
Black or African American	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Multiple	0 (0.0%)	4 (12.9%)	0 (0.0%)	4 (8.0%)
White	15 (93.8%)	26 (83.9%)	3 (100.0%)	44 (88.0%)
Ethnicity				
Hispanic or Latino	3 (18.8%)	5 (16.1%)	1 (33.3%)	9 (18.0%)
Not Hispanic or Latino	13 (81.3%)	26 (83.9%)	2 (66.7%)	41 (82.0%)
Country				
Europe	12 (75.0%)	26 (83.9%)	2 (66.7%)	40 (80.0%)
North America	2 (12.5%)	0 (0.0%)	1 (33.3%)	3 (6.0%)
South America	2 (12.5%)	5 (16.1%)	0 (0.0%)	7 (14.0%)

Source: Clinical Reviewer's Analysis

Adequacy of the safety database:

During the pre-NDA meeting on 3 April 2018, a safety database of 300 subjects receiving the study drug at the proposed dose and duration for the proposed indications was requested by the FDA. Though the submitted safety database is somewhat smaller than this, it was deemed adequate given the extensive clinical experience with imipenem since its approval in 1985 for the two indications being requested under this NDA, namely cUTI and cIAI. (b) (4)

(b) (4)

7.4.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The overall quality of submitted data was adequate. A data traceability assessment was conducted in conjunction with the JumpStart service provided through the Office of Computational Sciences (OCS). There were minor findings identified through this assessment with the majority having either minimal or no impact on data analysis.

For additional assessment of the quality of the initial data collection and integrity, an Office of

Scientific Investigations (OSI) consult was obtained and seven clinical sites were selected for inspection for studies PN003, PN004, and PN013. The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the proposed indications. (see Section 4.1).

Categorization of Adverse Events

Adverse events (AEs) were collected from the first day of IV trial treatment (Day 1) through 14 days after completion of trial treatment in studies PN003, PN004 and PN013. In PN003, the cUTI trial where transition to ciprofloxacin was permitted after initial IV therapy, completion of trial treatment included completion of IV trial treatment plus subsequent oral ciprofloxacin treatment where applicable.

Serious adverse event was defined as an AE occurring at any dose that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged existing inpatient hospitalization, was a congenital anomaly/birth defect or was deemed an important medical event. In PN003 and PN004, cancer and overdose were also considered SAEs.

In terms of timing, AEs were categorized by the Applicant in three ways in the CSRs for the three trials, as well as the ISS datasets:

- AEs with onset with during trial treatment through 14 days after end of trial treatment,
- AEs with onset during IV trial treatment only and,
- AEs with onset at any point during the trial.

Events of clinical interest (ECI) were defined as follows:

- AST or ALT value ≥5 X ULN or
- AST or ALT value ≥3 X ULN accompanied by a total bilirubin value ≥2 X ULN and an alkaline phosphatase value <2 X ULN

In scenarios where a subject signed a consent form, then experienced an AE that resulted in exclusion from the trial or was the result of a protocol-specific intervention, the AE was reported. If there were SAEs that occurred outside of the 14-day follow-up period but were considered by the investigator to be possibly, probably or definitely related to trial treatment, they were also reported. AEs were coded with MedDRA Version 18.0 in PN003, Version 17.0 in PN004, Version 18.1 in the ISS database and Version 20.0 in PN013.

Reviewer comment: For the purposes of the Agency's analysis, AEs and SAEs were analyzed regardless of whether they were deemed related or unrelated by investigators to study drug. This resulted in a higher number of AEs being reported in the Agency analysis, especially for common AEs, for example GI-related AEs such as diarrhea or nausea. For AEs where a relationship to the study drug was questionable given the mechanism of action and known

outcomes of the components of the study drug, the CSRs and narratives, where available, were reviewed to adjudicate the relationship between the AE and the study drug. When required, additional information including narratives and datasets were requested from the Applicant. Please refer to Section 7.4.4 for further details of the safety results including analysis of AEs.

Routine Clinical Tests

Routine blood and urine laboratory studies were collected as part of protocols for PN003, PN004 and PN013 and included, but were not limited to hematology tests (white blood cell count and differential, hemoglobin, hematocrit, platelet count), blood chemistry tests (albumin, blood urea nitrogen, calcium, bicarbonate, creatinine, glucose, electrolytes, serum protein, serum bilirubin, liver transaminases), urinalysis tests (protein, glucose, microscopic analysis).

Reviewer Comment: Due to a potential pancreatitis signal, a request was made to the Applicant to provide all available baseline and post-baseline lipase and amylase values for the safety population for the three trials. Per the Applicant's response dated 22 Feb 2019, the cIAI (PN004) was the only study in the IMI/REL program in which lipase and amylase values were measured as part of the routine safety laboratory panel. Datasets of all available baseline and postbaseline central laboratory results for amylase and lipase were provided with this response. Please refer to Section 7.4.4 for adverse event results related to specific laboratory values by study.

7.4.4 Safety Results

Summary

cUTI and cIAI trials

During the follow-up period, there were 3 deaths, all of which occurred in the IMI/REL 125mg treatment arm in study PN004 (cIAI). Overall, more SAEs occurred in the IMI/REL 125mg (5.6%, 12/215) as compared to the IMI/REL 250mg (3.2%, 7/216) and the IMI/Placebo (5.1%, 11/214) treatment arms. There was no difference in discontinuations of study drug due to SAEs between subjects receiving IMI/REL and IMI/Placebo. Two subjects discontinued study drug in the IMI/REL 250mg and in the IMI / Placebo arm and 3 subjects discontinued study drug due to SAEs in the IMI/REL 125mg arm.

Table 52. Safety Summary, PN003 and PN004, Safety Population

Event	IMI/ REL 250mg (N=216) n (%)	IM/REL 125mg (N=215) n (%)	IMI/Placebo (N=214) n (%)
Deaths	0 (0%)	3 (1.4%)	0 (0%)
SAEs	7 (3.2%)	12 (5.6%)	11 (5.1%)

Discontinuations of Study Drug due to SAEs	2 (0.9%)	3 (1.4%)	2 (0.9%)
All TEAEs	85 (39.4%)	84 (39.1%)	77 (36%)
D/c study drug d/t TEAEs	4 (1.9%)	6 (2.8%)	5 (2.3%)
TEAEs related to study drug[1]			
Mild	40 (18.5%)	45 (20.9%)	42 (19.6%)
Moderate	38 (17.6%)	31 (14.4%)	28 (13.1%)
Severe	7 (3.2%)	6 (2.8%)	6 (2.8%)

Source: Clinical Reviewer's Analysis
[1]1 case missing severity in IMI + Placebo arm and 2 cases missing severity in IMI + REL 125mg arm

Study PN013

Deaths occurred in 2 (6.5%) subjects in Treatment Group 1 (IMI/REL plus Placebo) and 3 (18.8%) subjects in Treatment Group 2 (CMS + IMI). SAEs were reported in 3 (9.7%) subjects in Treatment Group 1 and 5 (31.3%) subjects in Treatment Group 2, of which none were deemed treatment-related by the study investigators and the reviewer. There were also no discontinuations of study drug due to SAEs in either treatment arm. There were 3 (18.8%) discontinuations due to non-serious treatment-emergent AEs in Treatment Group 2 and none in Treatment Group 1. Most subjects in both treatment groups experienced AEs during the follow up period; 22 (71%) subjects reported AEs in Treatment Group 1 and 13 (81.3%) subjects in Treatment Group 2 reported AEs. Most reported AEs were mild in both groups.

Table 53. Safety Summary for the Randomized Arms of PN013, Safety Population

Event	**Treatment Group 1: IMI/REL 250 mg + Placebo for CMS N=31**	**Treatment Group 2: CMS + IMI N=16**
Deaths	2 (6.5%)	3 (18.8%)
SAEs	3 (9.7%)	5 (31.3%)
Discontinuations of Study Drug due to SAEs	0 (0%)	0 (0%)
All TEAEs	22 (71%)	13 (81.3%)
D/c study drug d/t TEAEs	0 (0%)	3 (18.8%)
TEAEs Severity		
Mild	13 (41.9%)	6 (37.5%)
Moderate	4 (12.9%)	2 (12.5%)
Severe	5 (16.1%)	5 (31.3%)

Source: Clinical Reviewer's Analysis

Reviewer comment: There were more adverse events overall reported in Treatment Group 2 (CMS + IMI) compared to Treatment Group 1 (IMI/REL + Placebo). This included deaths, SAEs, and discontinuations due to AEs, which were all reported more frequently in Treatment Group 2. This is consistent with the known toxicities associated with CMS. However, due to the small sample size of this trial, no definitive conclusions can be drawn regarding differences between the two treatment groups.

Deaths

Overall, there were 11 deaths in all IMI/REL clinical trials. There were no deaths in the Phase 1 trials. Five deaths occurred in studies PN003 and PN004 and six deaths occurred in study PN013. Of the five deaths that occurred in studies PN003 and PN004, three occurred during the follow-up period and two occurred outside the 14-day follow-up period.

Table 54. Deaths in All IMI/REL Clinical Trials, Safety Population

Deaths in PN003 and PN004	
During the follow-up period	
cUTI (Study PN003)	0
cIAI (Study PN004)	3 (1.4%) IMI/REL 125mg
Outside the follow-up period	
cUTI (Study PN003)	2 (0.9%) IMI/REL 250mg
cIAI (Study PN004)	0
Total in PN003 and PN004	*5*
Deaths in Study PN013	
In the randomized arms	2 (6.5%) IMI/REL + Placebo 3 (18.8%) IMI + CMS
In the open label arm	1
Total in PN013	6
All deaths during IMI/REL Development	11

Source: Clinical Reviewer's Analysis
**There were no deaths in Phase 1 trials*

The deaths that occurred in studies PN003 and PN004 during the follow-up period are summarized in Table 55.

Table 55. Deaths in studies PN003 and PN004 That Occurred During Follow-Up Period, Safety Population

Treatment Group	**Subject**	**Age**	**Gender**	**Trial**	**Baseline Organism**	**Duration of Treatment**	**Day of Death (Study Day)**	**Cause of Death**

MK-7655 125mg + IMI	1	72	M	cIAI(P004)	*E. coli*	2 days	D 3	Septic shock
MK-7655 125mg + IMI	2	72	M	cIAI (PN004)	*E. coli*	3 days	D 14	Intestinal infarction
MK-7655 125mg + IMI	3	76	F	cIAI (PN004)	*E. coli*	3 days	D3	Ventricular fibrillation

Source: Clinical Reviewer's Analysis

All three deaths reported during the follow-up period occurred in study PN004 in the IMI + REL 125mg treatment group. There were no deaths in the IMI + Placebo arms in studies PN003 and PN004.

The two deaths occurring after the follow-up period occurred in study PN003, in the IMI/ REL 250mg treatment group. One death was due to progression of renal cancer 32 days following completion of study drug and another due to cardiac arrest 28 days following completion of study drug.

The death from renal cancer progression occurred in a 72-year-old female patient who received IMI/REL 250mg for 10 days for a diagnosis of cUTI. She had a complicated urogenital history including radical nephrectomy of her right kidney, left ureteral stent insertion, urolithiasis and right renal carcinoma with rapid metastatic progression. Approximately 2 weeks later after completing study treatment she experienced an SAE of pyelonephritis and was admitted to the hospital and initiated on imipenem/cilastatin. She recovered from the acute pyelonephritis, but it was noted that she continued to have rapid progression of renal carcinoma with metastases to the liver and lung. She died 32 days following completion of study drug.

The second subject was an 83-year-old male who began IMI/REL 250mg for a cUTI and received the study drug for 8 days and completed treatment. The patient had a medical history of hypertension and heart failure. Approximately 2 weeks later the patient died from cardiac arrest. He was not hospitalized for the event and received no emergency medication.

Reviewer Comment: The timing of study drug administration in these two patients and the timing of their deaths does not suggest a relationship with study drug. Both deaths occurred several weeks following the patient's completion of the study drugs. There is a clear etiological cause in the patient who died from renal cancer progression and it is unlikely related to the

study drug. For the second patient who died from cardiac arrest, although a cardiac arrest was diagnosed, we do not have the details as to what may have led to the cardiac arrest, though the patient did have predisposing factors including hypertension and heart failure. Of note, the patient was on concomitant medications of isoniazid, rifampin, pyrazinamide and ethambutol at the time of his death, suggesting a possible diagnosis of active tuberculosis, though this diagnosis was not included in the narratives provided or CRF and should have been an exclusion criterion.

Three deaths reported during the follow-up period were due to ventricular fibrillation on Day 3, intestinal infarction on Day 14 (study drug discontinued on Day 3 due to decrease in creatinine clearance) and septic shock on Day 3 and are summarized in Table 55.

One death occurred while the subject was on the study drug (Subject 3: Table 55). The subject was a 76-year-old female with a diagnosis of complicated cholecystitis and generalized peritonitis who began treatment with IMI/REL 125mg on D1. Of note a cholecystectomy was performed on D -1, one day prior to randomization. She grew multiple organisms including *E. coli*, *K. oxytoca*, and *E. faecalis* from her surgical culture. She developed paroxysmal atrial fibrillation on the same day study drug was initiated for which amiodarone was started. Her cardiovascular status worsened over the subsequent 2 days with ineffective circulation and apnea with ventricular fibrillation. Resuscitation was initiated but was unsuccessful. Her concomitant medications at the time of death included duloxetine and trazodone. Autopsy findings revealed acute cardiac failure and atherosclerosis.

The other two deaths occurred after the study drug had been discontinued.

Subject 1 was a 72-year-male with a diagnosis of perforated colon and peritonitis who began treatment with IMI/REL 125mg on D1. He underwent open laparotomy with sigmoid colon resection and colostomy on the same day and was also found to have a malignant tumor of the colon. On D2 he had an SAE of acute renal failure, the study drug was withdrawn on the same day and renal replacement therapy was started. A few hours later an SAE of septic shock was recorded, and he required vasopressors. He died on D3 due to septic shock.

Subject 2 was a 72-year-old male with a perforated ileum and colon who began treatment with IMI/REL 125mg on D1. His past medical history included hypertension. He underwent surgery on day of study drug initiation with resection of the small bowel and right colon with bowel-colon anastomosis. On D2, he experienced an AE of decreased creatinine clearance, which was considered related to study drug and on D3, elevations of AST and ALT, also deemed related to study drug. The study drug was discontinued on D3 due to the decrease in creatinine clearance. On D5, AST elevation resolved and on D9, the ALT elevation resolved. On D14, the patient experienced an SAE of intestinal infarction, which resulted in cardiorespiratory arrest and death.

All deaths reported in studies PN003 and PN004 occurred in subjects > 70 years of age.

Reviewer Comment: After assessing the narratives and CRFs in detail, none of the deaths in the PN003 and PN004 appear to be due to treatment failure or because of the treatment itself. Subjects 1 and 2 experienced serious complications of their underlying disease process, which led to death. The only subject that experienced an event possibly unrelated to her underlying infectious process was Subject 3, who experienced paroxysmal atrial fibrillation (presumably a new diagnosis), followed by cardiovascular decompensation leading to ventricular fibrillation and death. No clear cardiovascular signal emerged from our analysis of the data and cardiovascular events were not reported in nonclinical studies. Cardiovascular events, including arrythmias, are not commonly reported with imipenem/cilastatin use. Palpitations and tachycardia are the only cardiovascular events reported and listed in the imipenem/cilastatin label and occur in less than 0.2% of patients.

Study PN013

In PN013, there were a total of six deaths. Five deaths occurred during the randomized portion of the trial, 6.5% (2/31) subjects in Treatment Group 1 (IMI/REL + Placebo to CMS) and 18.8% (3/16) subjects in Treatment Group 2 (IMI + CMS). One death occurred in the open-label arm of the study (Treatment Group 3).

There were no deaths in subjects with cUTI. Three deaths occurred in subjects with HABP/VABP and 2 deaths occurred in subjects with cIAI. In the HABP/VABP population, the AEs leading to death were lung infection, subarachnoid hemorrhage, and ventricular tachycardia. A summary of deaths reported in Study PN013 can be found in Table 56.

Reviewer Comment: The rate of death in study PN013 was greater than that in studies PN003 and PN004. This is likely due to severity of illness in patients enrolled in PN013 as inclusion criteria were less restrictive, subjects had to have a baseline imipenem-resistant pathogen and subjects with HABP/VABP were enrolled.

Table 56. Deaths in PN013, Safety Population

Treatment Group	Subject	Age	Gender	Infection Site	Baseline Organism	Duration of Treatment	Day of Death	Cause of Death
Treatment Group 1: IMI/REL + Placebo for CMS	1	59	M	cIAI	*C. freundii*	3d	D 3	Worsening PNA, Systemic inflammatory response syndrome
Treatment Group 1: IMI/REL +	2	75	M	VABP	*P. aeruginosa*	11d	D 17	Lung infection

Placebo for CMS								
Treatment Group 2: CMS + IMI	3	80	M	cIAI	*P. aeruginosa*	21d	D 26	Septic shock
Treatment Group 2: CMS + IMI	4	54	M	VABP	*P. aeruginosa*	3d	D 8	Subarachnoid haemorrhage
Treatment Group 2: CMS + IMI	5	22	F	VABP	*P. aeruginosa*	4d	D 4	Ventricular tachycardia
Treatment Group 3: IMI/REL	6	24	F	HABP	*P. aeruginosa*	8d	D8	Septic shock

Source: Clinical Reviewer's Analysis

Subject 1 was screened for the study due to perforated colon on Day -1 and a peritoneal fluid specimen that grew *C. freundii* resistant to IMI but susceptible to IMI/REL and colistin. He was a 59-year-old male with an extensive past medical history including recurrent rectal carcinoma (s/p anterior resection), partial small resection, osteomyelitis, chronic pain, alcohol abuse, and emphysema. Prior to study enrollment, he had been on multiple antibacterial drugs during his hospital course including piperacillin/tazobactam (D-15 to -8), ciprofloxacin (D-8 to -3), erythromycin (D-8 to 1), metronidazole (D-8 to 1), meropenem (D-7 to 4), Fosfomycin (D-4 to 4), ceftazidime/avibactam (D-1 to 1). With the exception of meropenem which was indicated for pneumonia, the remainder of the antibacterial drugs were listed as being used for infection prophylaxis. On D1 he was randomized to IMI/REL plus Placebo to CMS and the study drug was initiated. On the same day he was noted to have increased oxygen demand, decreased urine output and delirium, and was intubated with a diagnosis of pneumonia (not the qualifying diagnosis for the study). By D3 (OTX visit), the patient has overall worsening conditions with respiratory insufficiency, sepsis and organ failure leading to transition to palliative care. He died on the same day. Two SAEs were reported for this patients, worsening pneumonia and systemic inflammatory syndrome.

Reviewer Comment: The patient's extensive past medical history and prolonged hospital course with multiple antimicrobials used and multiple complications suggest that his death was not related to the study medication or failure of the study drug. His decompensation from sepsis/septic shock and pneumonia leading to intubation was noted on the same day the study drug IMI/REL was initiated. He was transitioned to palliative care 3 days later. The timing does not suggest relationship to the study drug.

Subject 2 was screened for the study on D1 due to a bronchial lavage fluid specimen collected on D -6, which grew *Pseudomonas aeruginosa* susceptible to IMI/REL and colistin but resistant to IMI. He was a 75-year-old male admitted to the hospital with multiple rib fractures and a

hemopneumothorax and subsequently developed VABP. He was initiated on the study drug, IMI/REL + placebo to colistin, on D1. On D3 and D5, the patient's clinical response appeared to have improved. The last dose of IMI/REL was on D11 (EOT visit). The patient's clinical response was deemed "improved." He remained on mechanical ventilation, but with improved tachypnea and dyspnea. A repeat tracheal aspirate culture grew *E. aerogenes* susceptible to IM/REL, colistin and IMI. On a D14 follow up visit (EFU visit), the patient had developed fever and worsening tachypnea with chest radiograph showing bilateral infiltrated. On D16, another tracheal aspirate grew *P. aeruginosa* and *E. aerogenes* susceptible to IMI/REL, colistin and IMI. Information on whether this patient was re-initiated on antibacterial drugs was not available. The subject died from worsening respiratory failure on D17. SAE of pulmonary infection was reported on D17.

Reviewer comment: The patient appears to have been at risk for recurrent pulmonary infection due to his intubated status. The initial infection for which IMI/REL was initiated on D1 appears to have improved by the D11 (EOT visit), however he grew a new organism, E. aerogenes, susceptible to IMI (thus not a qualifying organism for the study). It is not clear if he was initiated on new antibacterial drugs. The patient's prolonged intubation is likely the cause of the pneumonia leading to death. The death is unlikely related to the study drug or its failure in this case.

Subject 3 was screened for the study on D1 due to a cIAI with an intra-abdominal abscess collected on D-5 growing *P. aeruginosa* resistant to IMI but susceptible to IMI/REL and colistin. He was an 80-year-old male with an extensive past medical history including history of hepatic failure, cholangitis, extrahepatic bile duct tumor, s/p endoscopic retrograde cholangiopancreatography (ERCP) with placement of percutaneous biliary drain, s/p pancreatoduodenectomy, acute renal failure and abdominal infection with *Candida albicans* and *Enterococcus faecalis*. He was initiated on the comparator regimen CMS + IMI on D1. The last dose of treatment with CMS + IMI was on D21 (EOT visit). Clinical response was deemed improved at this visit. On D24, the patient developed septic shock, with hemodynamic deterioration, increased creatinine, respiratory failure, neurologic decline, bleeding from abdominal wound and rising liver tests. Meropenem, colistin and anidulafungin were initiated on D25 for septic shock and the family elected for no advanced resuscitation at this time. The patient died on D25 (EFU visit) due to septic shock.

Reviewer comment: This was a very complicated and severely ill patient with multiple underlying comorbidities and complications during his hospitalization. While difficult to ascertain which of the many complications led to his eventual death, there is no clear causal link to the comparator regimen (CMS + IMI) regarding timing or treatment failure. While acute renal failure was a prominent feature of his septic shock, this could have been related to his overall multiorgan failure and/or administration of colistin or both. Of note, this patient did meet criteria for a possible drug induced liver injury (DILI) case on D17, due to rising liver tests. This is discussed further in section 7.4.5, under study PN013.

Subject 4 was a 54-year-old male diagnosed with VABP on D1 with an isolate of *P. aeruginosa* intermediate to IMI but susceptible to colistin and IMI/REL. He was admitted to the hospital on D-54 with subarachnoid hemorrhage (SAH) treated with vascular stenting. He was randomized to the comparator regimen, CMS + IMI, and received the first dose on D1. The patient had a serum creatinine of 2.96 mg/dL on D1, which worsened by D3 to 3.3 mg/dL. CMS + IMI was discontinued on D3 due to increased blood creatinine. The clinical response to study medication was deemed as failure and the patient died due to hypoxic brain injury secondary to another episode of SAH that occurred on D7.

Reviewer comment: The SAE of SAH leading to death was unlikely to be related to the study drug.

Subject 5 was a 22-year-old female with a history of hypertension admitted to the hospital on D-39 with cerebral hemorrhage. She required mechanical ventilation and subsequently developed VABP. A tracheal aspirate grew *P. aeruginosa* susceptible to IMI/REL and colistin and resistant to IMI. She was randomized to the comparator regimen, CMS + IMI, and received her first dose on D1. At screening she had a creatinine of 3.0 mg/dL, which had risen to 3.84 mg/dL by D3. She underwent hemodialysis on D3 and on D4 had an event of ventricular tachycardia with cardiac arrest. She underwent cardioversion and resuscitation but died on D4. The ventricular tachycardia and cardiac arrest were attributed to hypocalcemia (calcium 7.2 mg/dL on D1 and 8.2 mg/dL on D3).

Reviewer comment: The reported ventricular tachycardia attributed to hypocalcemia in this case is questionable as the calcium was not severely low and also appeared to have increased at the time of the ventricular tachycardia leading to the cardiac arrest. However, it is likely that given her ongoing renal failure and initiation of hemodialysis a day prior (D3), she likely had other electrolyte imbalances as well. Her creatinine was already elevated at the time of initiation of CMS + IMI (3.0 mg/dL), which had increased 2 days following initiation of CMS + IMI to 3.84 mg/dL. While it is difficult to exclude a role of CMS + IMI in her rising creatinine, the bulk of the renal injury had occurred prior to initiation of CMS + IMI.

Subject 6 was a 24- year- old female with a history of cystic fibrosis (CF), diabetes, aspergillosis and was enrolled in the open-label arm of the trial. She was hospitalized on D-15 with a CF exacerbation and grew *P. aeruginosa* from a respiratory specimen on D-4. She was initiated on IMI/REL on D1 combined with inhaled colistin. The patient was intubated on D2 due to progressive respiratory failure. She had a tracheostomy placed on D7 but developed progressive hemodynamic instability and oliguria and was diagnosed with septic shock. She died on D8 and was on study medication at the time of death.

Reviewer comment: The patient had a prolonged hospitalization with CF, with progressively resistant organisms being recovered from the sputum. She received multiple antibacterial drugs during the hospitalization, with both IV and inhaled formulations. Overall, I agree with the investigators that the reported events of septic shock and pneumonia with progressive

respiratory failure were unlikely related to the study drug, although the lack of efficacy of study treatment may have contributed to the outcome of death.

Overall, there was no clear causal link between either the study drug, IMI + REL, or the comparator regimen, CMS + IMI and the deaths occurred in trial PN013. This was partly due to the complicated and highly morbid status of the patients enrolled in the study and in particular of the six patients who died in the trial. It was difficult to ascertain the role, if any, of the trial treatments in the patient's death, however looking at the overall preponderance of evidence none of the six deaths appear related to the study drug or comparator regimen. Of the six deaths observed in PN013 five occurred in the randomized portion of the trial, while one death occurred in the open-label treatment arm.

Of the five deaths in the randomized portion, the majority were in the comparator arm, CMS + IMI, with 18.8% (3/16) patients dying in this study arm compared with 6.5% (2/31) patients dying in the IMI/REL arm. There was a wider age distribution of deaths in this trial compared to PN003 and PN004, likely due to the higher morbidity of the patients enrolled in this trial and the inclusion of HABP/VABP. Four of the six reported deaths were in patients with HABP/VABP. There were no deaths in patients with cUTI, which is consistent with the lower morbidity and mortality associated with this infection in general.

Two of the deaths occurred in very young patients, a 22- and 24-year-old females. The 22-year-old patient was admitted with a cerebral hemorrhage leading to a prolonged hospitalization with mechanical ventilation leading to VABP which is more likely to have caused the death rather than the study medication. The 24-year-old patient was a patient with CF with prolonged hospitalization with mechanical ventilation and progressive respiratory failure due to CF and VABP. There was no clear causal link between the study medication and the reported death, with the underlying disease process being the more likely culprit.

Serious Adverse Events

Studies PN003 and PN004

All Serious Adverse Events

Serious adverse events (SAEs) were analyzed in the pooled safety population for studies PN003 and PN004. Serious adverse events occurred in 4.7% (30/645) of subjects in the pooled safety population: 3.2% (7/216) of patients receiving IMI/REL 250mg, 5.6% (12/215) patients receiving IMI/REL 125mg, and 5.1% (11/214) of patients receiving IMI plus Placebo. There were more SAEs overall reported in the IMI/REL 125mg arm compared to IMI/REL 250mg arm.

Selected SAEs that were considered possibly related to study drug toxicities, regardless of whether deemed related by site investigator, are detailed in Table 57.

Table 57. Selected Serious Adverse Events in PN003 and PN004, Safety Population

System Organ Class MedDRA Preferred Term	IMI /REL any dose[1] N=431 n (%)	IMI/Placebo N=214 n (%)
Gastrointestinal disorders		
Diarrhea	2 (0.3%)	1 (0.1%)
Renal and urinary disorders		
Acute kidney injury	1 (0.1%)	0 (0.0%)
Cardiac disorders		
Ventricular fibrillation	1 (0.1%)	0 (0.0%)
Blood and lymphatic system disorders		
Thrombocytosis	0 (0%)	1 (0.5%)
Infections and infestations		
Clostridium difficile infection	1 (0.1%)	0 (0.0%)

Source: Clinical Reviewer's Analysis
[1]Includes IMI/REL 250mgIMI/REL 125mg

Reviewer comment: Although there were more overall SAEs reported in the IMI/REL 125mg compared to the IMI/REL 250mg arm, the overall numbers were small, limiting the ability to note any significant differences between specific reported SAEs or draw any conclusions. Of the selected SAEs reported above, diarrhea was reported in both treatment arms, 1 each in subjects receiving IMI/REL 125mg and IMI/REL 250mg. Acute kidney injury, C. difficile colitis and ventricular fibrillation were all reported in 1 subject each, all receiving IMI/REL 125mg. Due to the small numbers, the finding of more SAEs in the lower dose treatment arm is likely due to chance.

SAEs reported in the pooled ISS data, but not considered related to study drug toxicities and thus not reported in the above table (Table 57) included: duodenal ulcer, duodenal ulcer perforation, ileus paralytic, liver abscess, peritonitis, renal neoplasm, wound evisceration, abdominal abscess, acute respiratory failure, benign gastrointestinal neoplasm, cerebrovascular accident, cholelithiasis obstructive, glomerulonephritis rapidly progressive, intestinal infarction, intestinal obstruction, lung consolidation, mucinous adenocarcinoma or appendix, pleural effusion, post procedural bile leak, postoperative wound infection, procedural pain, pulmonary embolism, septic shock, small intestinal obstruction, urosepsis and wound dehiscence.

Each SAE listed above was reported by 1 subject except for the following SAEs:

- Diarrhea (3 total subjects, 2 subjects in IMI/REL group, 1 subject in IMI + Placebo group).
- Abdominal abscess (2 total subjects, 1 subject in IMI/REL group, 1 subject in IMI+ Placebo group).
- Pulmonary embolism (2 total subjects, both in the IMI + Placebo group).

Reviewer comment: Table 57 *summarizes SAEs in PN003 and PN004 possibly related to study drug toxicities regardless of causality as determined by investigator. Diarrhea, acute kidney injury (AKI), thrombocytosis and Clostridium difficile infection are all relevant AEs given our knowledge of AEs associated with IMI exposure. Relationship of the study drug to AKI was not possible to rule out given the timing of study drug administration to onset of AKI. Additionally, the CRF states the investigator discontinued the study drug due to the AKI. Relationship of C. difficile infection to the study drug was also not possible to rule out. The subject received study medication from 27 May to 1 June and onset of C. difficile was 9 June, therefore we felt it was plausibly related despite the investigator report to the contrary. The relationship between cardiac disorders and study drug toxicities seems less apparent, however were included in the table for completeness and possible additional exploration given the death associated with ventricular fibrillation in Study PN004.*

The remainder of the SAEs reported were each reported by one subject except for diarrhea, abdominal abscess and pulmonary embolism, which were reported by multiple subjects. These SAEs were not considered related to study drug toxicities and are likely related to the underlying condition leading to hospital presentation (i.e., cUTI, renal neoplasm, liver abscess) or due to complications during the hospitalization unlikely related to study drug (i.e., pulmonary embolism).

Of the three SAEs reported in more than one subject, diarrhea is a common AE associated with antibacterial drugs including IMI. Abdominal abscess is not related to drug toxicities but to the underlying condition or, potentially, the lack of efficacy of study drug. Pulmonary embolism, although reported in 2 subjects here, was reported in the comparator group and is not a known AE associated with IMI or other carbapenems.

Drug-related Serious Adverse Events

A total of 4 SAEs were considered drug-related by the site investigators. These SAEs are listed in Table 58. Of note per Applicant report, the causality of the event of ileus paralytic was changed from related to unrelated in response to a safety query during final reconciliation of SAE/CIOMS data. This change was reflected in the CIOMS report but was not captured in the clinical database per the Applicant and is thus also reflected in the Agency's analysis below.

Table 58. Related SAEs in PN003 and PN004, Safety Population

MedDRA Preferred Term	IMI/REL any dose[1] N=431 n (%)	IMI/Placebo N=214 n (%)
Diarrhea	1 (0.2%)	1 (0.5%)
Ileus paralytic[2]	1 (0.2%)	0 (0.0%)
Thrombocytosis	0 (0.0%)	1 (0.5%)

Source: Clinical Reviewer's Analysis
[1]Includes IMI/REL 250mgIMI/REL 125mg
[2]Later revised by Applicant as unrelated but not reflected in dataset (see discussion above)

Diarrhea occurred in 2 subjects and led to discontinuation of IV study drug in one of the two subjects, while thrombocytosis also led to discontinuation of IV trial treatment in the one subject in which it occurred (IMI + Placebo treatment group). No action was taken with respect to the IV trial treatment in the one subject that experienced paralytic ileus in the IMI/REL treatment group.

Reviewer comment: Of the total 33 distinct SAEs reported in PN003 and PN004, only 3 were considered drug-related by the Applicant initially, and ileus paralytic was later revised as unrelated. Therefore, only two SAEs were considered drug-related and these two were diarrhea, and thrombocytosis as listed above. Only two of the three reported cases of diarrhea were considered related by the Applicant. Thrombocytosis was noted in one subject, leading to discontinuation of the study treatment and a switch to levofloxacin. Platelets peaked at 1111 $10^3/\mu L$ 3 days after study treatment was discontinued, then down trended to near normal levels approximately 15 days after study treatment was discontinued. Thrombocytosis is a known and listed AE related to IMI and thus it is plausible this was related to the study treatment. In addition to the two SAEs deemed related to the study drug by the Applicant, this reviewer also included the SAEs listed in Table 57, which included acute kidney injury, C. difficile colitis and ventricular fibrillation as possibly drug-related and these are discussed above.

Study PN013

Serious adverse events occurred in 9.7% (3/31) subjects in Treatment Group 1 (IMI/REL + Placebo to CMS) and 31.3% (5/16) subjects in Treatment Group 2 (CMS + IMI). All 3 subjects receiving IMI/REL in the open-label, non-randomized Treatment Group 3 experienced an SAE.

With the exception of pneumonia and septic shock which occurred in two subjects each, no single reported SAE occurred in more than one subject.

Table 59. Serious Adverse Events (SAEs) Reported in PN013, Safety Population

		Treatment Group		
System Organ Class	**MedDRA Preferred Term**	**Treatment Group 1: IMI/REL 250 mg + Placebo for CMS N=31**	**Treatment Group 2: CMS + IMI N=16**	**Treatment Group 3: IMI/REL 250 mg N=3**
General disorders and administration site conditions	Systemic inflammatory response syndrome	1 (3.2%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	Acute kidney injury	1 (3.2%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	Ventricular tachycardia	0 (0.0%)	1 (6.3%)	0 (0.0%)
Gastrointestinal disorders	Duodenal perforation	0 (0.0%)	0 (0.0%)	1 (33.3%)
	Acute abdomen	0 (0.0%)	0 (0.0%)	1 (33.3%)
	Upper gastrointestinal haemorrhage	0 (0.0%)	1 (6.3%)	0 (0.0%)
Hepatobiliary disorders	Hepatic haematoma	0 (0.0%)	0 (0.0%)	1 (33.3%)
Infections and infestations	Escherichia urinary tract infection	0 (0.0%)	0 (0.0%)	1 (33.3%)
	Lung infection	1 (3.2%)	0 (0.0%)	0 (0.0%)
	Pneumonia	0 (0.0%)	0 (0.0%)	2 (66.7%)
	Septic shock	0 (0.0%)	1 (6.3%)	1 (33.3%)
Injury, poisoning and procedural complications	Subarachnoid haemorrhage	0 (0.0%)	1 (6.3%)	0 (0.0%)
	Abdominal wound dehiscence	0 (0.0%)	0 (0.0%)	1 (33.3%)
Investigations	Alanine aminotransferase increased	0 (0.0%)	1 (6.3%)	0 (0.0%)
	Aspartate aminotransferase increased	0 (0.0%)	1 (6.3%)	0 (0.0%)

	Blood alkaline phosphatase increased	0 (0.0%)	1 (6.3%)	0 (0.0%)
Nervous system disorders	Generalized tonic-clonic seizure	0 (0.0%)	0 (0.0%)	1 (33.3%)
Psychiatric disorders	Mental status changes	0 (0.0%)	0 (0.0%)	1 (33.3%)

Source: Clinical Reviewer's Analysis

Reviewer Comment: The only SAE of clinical relevance occurring in the randomized treatment arm (IMI/REL) of study PN013 is acute kidney injury (AKI). The other two reported SAEs are lung infection and SIRS, which are likely related to the underlying condition rather than the study drug. In the open-label treatment arm, there are two SAEs of interest including generalized tonic-clonic seizure and mental status changes. Seizures are a known AE associated with IMI, as are central nervous adverse reactions and are planned to be listed as a warning in the IMI/REL label. Renal injury is planned to be listed as an adverse reaction. The remainder of the reported SAEs are likely related to the underlying condition rather than the study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

Studies PN003 and P004

10 subjects (2.3%) in the IMI/REL arms and 5 subjects (2.3%) in the IMI + Placebo arm discontinued the study drug. Table 60 lists the adverse events reported in subjects who discontinued the study drug. AEs considered related to study drug and leading to discontinuation occurred in 4 subjects (0.9%) in the IMI/REL arms and 4 subjects (1.9%) in the IMI + Placebo arm.

Table 60. Discontinuations by Adverse Event in PN003 and PN004, Safety Population

MedDRA Preferred Term	**IMI/REL any dose[1] N=431 n (%)**	**IMI/Placebo N=214 n (%)**
Acute kidney injury	1 (0.2%)	0 (0.0%)
Alanine aminotransferase increased	0 (0.0%)	1 (0.5%)
Creatinine renal clearance decreased	1 (0.2%)	0 (0.0%)
Diarrhea	2 (0.5%)	1 (0.5%)
Dizziness	0 (0.0%)	1 (0.5%)
Duodenal ulcer perforation	1 (0.2%)	0 (0.0%)
Intestinal obstruction	0 (0.0%)	1 (0.5%)
Nausea	1 (0.2%)	1 (0.5%)
Pyrexia	1 (0.2%)	0 (0.0%)
Rash	1 (0.2%)	0 (0.0%)

Thrombocytosis	0 (0.0%)	1 (0.5%)
Ventricular fibrillation	1 (0.2%)	0 (0.0%)
Vomiting	1 (0.2%)	0 (0.0%)
Total Subjects	10 (2.3%)	5 (2.3%)

Source: Clinical Reviewer's Analysis
[1]*Includes IMI/REL 250mg and IMI/REL 125mg*

The AEs leading to discontinuation and considered related to study included:

- Alanine aminotransferase increased (1 subject, IMI plus Placebo arm)
- Creatinine renal clearance decreased (1 subject, IMI/REL arm)
- Diarrhea (1 subject, IMI/REL arm, 1 subject, IMI plus Placebo arm)
- Nausea (1 subject, IMI/REL arm, 1 subject, IMI plus Placebo arm)
- Rash (1 subject, IMI/REL arm)
- Thrombocytosis (1 subject, IMI plus Placebo arm).

Reviewer comment: There were no specific patterns or differences noted in terms of discontinuations between the study arms. Gastrointestinal adverse events were the most common reasons for discontinuation and include diarrhea, nausea and vomiting. Of note, AEs leading to discontinuations in the IMI/REL 250mg arm included diarrhea, duodenal ulcer perforation, pyrexia and rash and in the IMI/REL 125mg arm included AKI, creatinine renal clearance decreased, diarrhea, nausea, ventricular fibrillation and vomiting. AEs leading to discontinuation in more than one subject included diarrhea and nausea. Diarrhea led to discontinuation in 3 subjects (2 subjects IMI/REL arm, 1 subject IMI + Placebo arm) and was considered related to the study drug in 2 of those subjects as described above. Nausea lead to discontinuation in 2 subjects (1 subject IMI/REL arm, 1 subject IMI + Placebo arm) and was considered related to the study drug in both subjects. There were no additional AEs that led to discontinuation in more than one subject.

Study PN013

There were no discontinuations of IV study drug in Treatment Group 1 (IMI/REL plus placebo) due to adverse events in Study PN013 (Table 61). In the randomized groups, all discontinuations of IV study drug were reported in Treatment Group 2 (CMS + IMI). There was also one discontinuation in the open-label, non-randomized Treatment Group 3 (IMI/REL). Two discontinuations in Treatment Group 2 were due to changes in renal function (blood creatinine increased, and creatinine renal clearance decreased) and one discontinuation was due to *Stenotrophomonas* infection. In the open-label treatment group, the one discontinuation was due to generalized tonic-clonic seizure.

Table 61. Adverse Events Leading to Discontinuation of IV Therapy in Study PN013, Safety Population

	Treatment Group		
System Organ Class Preferred Term	**Treatment Group 1: IMI/ REL + Placebo N=31 n (%)**	**Treatment Group 2: CMS + IMI N=16 n (%)**	**Treatment Group 3: IMI/REL N=3 n (%)**
Investigations			
Blood creatinine increased	0 (0%)	1 (6.3%)	0 (0.0%)
Creatinine renal clearance decreased	0 (0%)	1 (6.3%)	0 (0.0%)
Nervous System Disorders			
Generalized tonic-clonic seizure	0 (%)	0 (0.0%)	1 (33.3%)
Infections and Infestations			
Stenotrophomonas infection	0 (0%)	1 (6.3%)	0 (0.0%)
Total	**0 (0%)**	**3 (18.8%)**	**1 (33.3%)**

Source: Clinical Reviewer's Analysis

Reviewer comment: The sample size of this study was small and limits the interpretation of discontinuations observed. No discontinuations were observed in the randomized treatment arm, Group 1: IMI/REL compared to 3 discontinuations in the comparator arm, Group 2: CMS + IMI. The single discontinuation in the open-label treatment group was due to a generalized tonic-clonic seizure, which is a known serious adverse reaction associated with IMI and is planned to be listed as a warning in the label.

Significant Adverse Events

Studies PN003 and PN004

- Central Nervous System: CNS adverse events including seizures, confusional states and myoclonic activity have been reported during treatment with imipenem/cilastatin, a component of IMI/REL and are included as a warning in the label for imipenem/cilastatin.
    - There were no seizures reported in Study PN003 and PN004.

  - Central Nervous System Disorders (Neurological) (includes slow speech, somnolence) were reported in 2 subjects total, 0 subjects in IMI/REL treatment group and 2 subjects (0.9%) in IMI + Placebo treatment group.

  - Central Nervous System Disorders (Psychiatric) (includes agitation, apathy, confusional state, delirium, disorientation) were reported in 6 subjects total, 2 subjects (0.5%) in IMI/REL treatment group and 4 subjects (1.9%) in IMI + Placebo treatment group.

- *C. difficile* Colitis

  - *C. difficile* colitis and *C. difficile* infection were reported in a total of 3 subjects (0.7%). All 3 AEs were reported in subjects receiving IMI/REL and 0 were reported in subjects receiving IMI + Placebo.

- Serious hypersensitivity reaction

  - There were no serious hypersensitivity reactions including anaphylaxis reported in Study PN003 and PN004.

Reviewer Comment: There were no seizures reported in PN003 and PN004. Central nervous system (CNS) disorders were pooled by several AE terms under the general grouping of neurological and psychiatric. This was done to allow for a simplified and more robust grouping of central nervous system adverse reactions, which are known to be associated with IMI. CNS disorders were seen in the IMI/REL arm, as well as the IMI arm, which is expected given the known association with IMI. Slightly more CNS-related AEs were noted in the IMI group, however this is likely due to chance rather than due to a protective effect from REL. CNS disorders are planned to be included as a warning in the IMI/REL label, as well as listed in ***Section 6 Adverse Reactions*** *of the label.*

All three cases of C. difficile infection were reported in the IMI/REL 125mg arm, however this is likely due to chance as C. difficile infection is known to be associated with IMI exposure. C. difficile infection is planned to be listed as a warning in the IMI/REL label.

Hypersensitivity reactions including phlebitis, rash and pyrexia were reported in PN003 and PN003, however none of the reactions were severe or serious. There were no cases of anaphylaxis or other systemic hypersensitivity reported.

Study PN013

- Central Nervous System

  - One subject experienced an AE of generalized tonic-clonic seizure in Treatment Group 3 (IMI/REL). The subject had a reported inadvertent administration of additional doses of non-study imipenem prior to onset of the seizure.

- *C. difficile* Colitis
  - There were no cases of *C. difficile* colitis reported in Study PN013.
- Serious hypersensitivity reaction
  - There were no serious hypersensitivity reactions including anaphylaxis reported in Study PN013.

Reviewer comment: Seizure is a known AE associated with IMI exposure. No cases of C. difficile infection were reported in this study; however, the sample size is small. Serious hypersensitivity reactions were also not reported, however less serious reactions reported included phlebitis and rash, which are discussed elsewhere. Adverse reactions observed in this trial were not significantly different from those observed in PN003 and PN004 and were consistent with the known safety profile of imipenem (see Section 10: Labeling Recommendations).

Treatment Emergent Adverse Events

Studies PN003 and PN004

The most common AEs reported in PN003 and PN004 are gastrointestinal disorders including nausea, diarrhea and vomiting (Table 62). 27 subjects (6.2%) in the IMI/REL treatment arms and 12 subjects (5.6%) in the IMI/Placebo arms reported nausea; 21 subjects (4.8%) in the IMI/REL treatment arms and 9 subjects in the IMI/Placebo treatment arms (4.2%) reported diarrhea; 17 subjects (3.9%) in the IMI/REL treatment arms and 4 subjects (1.9%) in the IMI/Placebo treatment arms reported vomiting. Additional AEs of interest include *C. difficile* infection, liver enzyme abnormalities, renal disorders, hematology disorders and hypersensitivity-type reactions. To allow a more accurate analysis of similar preferred terms, some of these terms were pooled together to allow for a more meaningful analysis. A summary of pooled terms can be found in Table 63.

Table 62. Treatment Emergent Adverse Events (TEAEs) Occurring in ≥0.5% subjects in the ISS population (Studies PN003 and PN004)

System Organ Class	MedDRA Preferred Term	IMI/REL any dose[1] N=431 n (%)	IMI/Placebo N=214 n (%)
Gastrointestinal disorders	Nausea	27 (6.3%)	12 (5.6%)
	Diarrhea	21 (4.9%)	9 (4.2%)

	Vomiting	17 (3.9%)	4 (1.9%)
	Constipation	3 (0.7%)	1 (0.5%)
	Abdominal pain upper	3 (0.7%)	0 (0.0%)
	Abdominal pain	2 (0.5%)	0 (0.0%)
	Gastritis	2 (0.5%)	0 (0.0%)
	Salivary hypersecretion	0 (0.0%)	2 (0.9%)
	Tooth discoloration	2 (0.5%)	0 (0.0%)
Investigations	Alanine aminotransferase increased	13 (3.0%)	4 (1.9%)
	Aspartate aminotransferase increased	13 (3.0%)	3 (1.4%)
	Blood alkaline phosphatase increased	6 (1.4%)	2 (0.9%)
	White blood cells urine positive	2 (0.5%)	5 (2.3%)
	Blood creatinine increased	2 (0.5%)	3 (1.4%)
	Red blood cells urine positive	1 (0.2%)	2 (0.9%)
	Blood phosphorus decreased	0 (0.0%)	2 (0.9%)
	Blood potassium decreased	1 (0.2%)	1 (0.5%)
	Lipase increased	5 (1.2%)	4 (1.9%)
	Platelet count increased	6 (1.4%)	1 (0.5%)
	Bacterial test positive	2 (0.5%)	3 (1.4%)
	Protein urine present	1 (0.2%)	3 (1.4%)
	Neutrophil count increased	1 (0.2%)	2 (0.9%)
	Amylase increased	1 (0.2%)	1 (0.5%)
	Blood bilirubin increased	1 (0.2%)	1 (0.5%)
	Glucose urine present	0 (0.0%)	2 (0.9%)
	Blood pressure increased	1 (0.2%)	1 (0.5%)
	White blood cell count increased	2 (0.5%)	0 (0.0%)
Blood and lymphatic system disorders	Thrombocytosis	6 (1.4%)	2 (0.9%)
	Anemia	3 (0.7%)	3 (1.4%)
	Iron deficiency anemia	2 (0.5%)	0 (0.0%)
	Leukocytosis	2 (0.5%)	0 (0.0%)

	Thrombocytopenia	0 (0.0%)	2 (0.9%)
Cardiac disorders	Atrial fibrillation	4 (0.9%)	0 (0.0%)
	Cardiac failure congestive	2 (0.5%)	0 (0.0%)
	Tachycardia	0 (0.0%)	2 (0.9%)
General disorders and administration site condition	Pyrexia	5 (1.2%)	3 (1.4%)
	Oedema peripheral	5 (1.2%)	0 (0.0%)
	Infusion site phlebitis	3 (0.7%)	0 (0.0%)
	Impaired healing	1 (0.2%)	1 (0.5%)
	Infusion site erythema	2 (0.5%)	0 (0.0%)
Infections and infestations	Postoperative wound infection	5 (1.1%)	5 (2.3%)
	Bacteriuria	3 (0.7%)	4 (1.9%)
	Pneumonia	4 (0.9%)	0 (0.0%)
	Abdominal abscess	1 (0.2%)	1 (0.5%)
	Clostridium difficile colitis	2 (0.5%)	0 (0.0%)
	Influenza	2 (0.5%)	0 (0.0%)
	Liver abscess	2 (0.5%)	0 (0.0%)
	Post procedural infection	0 (0.0%)	2 (0.9%)
	Respiratory tract infection viral	2 (0.5%)	0 (0.0%)
	Vulvovaginal mycotic infection	2 (0.5%)	0 (0.0%)
	Vulvovaginal candidiasis	2 (0.5%)	0 (0.0%)
Injury, poisoning and procedural complications	Seroma	6 (1.4%)	0 (0.0%)
	Wound dehiscence	1 (0.2%)	1 (0.5%)
Metabolism and nutrition disorders	Hyperkalaemia	3 (0.7%)	0 (0.0%)
	Decreased appetite	1 (0.2%)	1 (0.5%)
	Diabetes mellitus	1 (0.2%)	1 (0.5%)
Musculoskeletal and connective tissue disorders	Back pain	3 (0.7%)	1 (0.5%)
Nervous system disorders	Headache	14 (3.2%)	5 (2.3%)
	Dizziness	2 (0.5%)	1 (0.5%)
	Dysgeusia	2 (0.5%)	0 (0.0%)
Psychiatric disorders	Delirium	1 (0.2%)	2 (0.9%)
	Anxiety	2 (0.5%)	0 (0.0%)
	Depression	2 (0.5%)	0 (0.0%)
Renal and urinary disorders	Dysuria	2 (0.5%)	3 (1.4%)
	Urinary retention	1 (0.2%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	3 (0.7%)	1 (0.5%)

	Cough	1 (0.2%)	1 (0.5%)
	Hydrothorax	1 (0.2%)	1 (0.5%)
	Oropharyngeal pain	0 (0.0%)	2 (0.9%)
	Pulmonary embolism	0 (0.0%)	2 (0.9%)
Skin and subcutaneous tissue disorders	Rash	4 (0.9%)	1 (0.5%)
	Hyperhidrosis	2 (0.5%)	0 (0.0%)
	Pruritus	1 (0.2%)	1 (0.5%)
Vascular disorders	Hypertension	8 (1.8%)	5 (2.3%)
	Phlebitis	4 (0.9%)	3 (1.4%)
	Hypotension	1 (0.2%)	1 (0.5%)

Source: Clinical Reviewer's Analysis
[1]*Includes IMI/REL 250mg and IMI/REL 125mg*

Reviewer Comment: Gastrointestinal AEs including nausea, vomiting and diarrhea were reported most frequently. This is consistent with AEs reported with IMI alone based on previous studies, as well as these two studies (PN003 and PN004). Vomiting was slightly more common with IMI/REL than IMI alone (3.9% vs. 1.9% respectively). There were no other major differences seen with gastrointestinal AEs. Additional AEs of interest include C. difficile infection, liver enzyme abnormalities, renal disorders, hematology disorders and hypersensitivity-type reactions. There were minor differences seen in ALT and AST increase between IMI/REL and IMI, with slightly more subjects in the IMI/REL treatment arms experiencing increases (ALT: 3.0% vs. 1.9%, AST: 2.8% vs. 1.4%). Hypersensitivity-type reactions including phlebitis, rash and pyrexia were slightly more common in IMI/REL compared to IMI, as was C. difficile colitis, however the differences were very small and are discussed further below with the pooled AE terms.

TEAEs by Pooled AE Terms

All reported AEs were reviewed for relevance. Similar AEs were pooled together under single unifying terms (Table 63).

Table 63. Pooled Adverse Event (AE) Terms by Similar Preferred Terms for PN003 and PN004

Pooled AE Term	**(Included MedDRA Preferred Terms**
Nausea	*nausea and vomiting*
Pancreatitis	*pancreatitis and pancreatitis acute*
Hyperglycemia	*hyperglycemia and blood glucose increased*
Renal injury	*blood creatinine increased, creatinine renal clearance decreased, acute kidney injury, renal impairment*
Bilirubin increased	*bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinemia*

Hemoglobin decreased	*hematocrit decreased, hemoglobin decreased*
Blood potassium decreased	*hypokalemia and blood potassium decreased*
Blood phosphorus decreased	*hypophosphatemia and blood phosphorus decreased*
Clostridium difficile infection	*Clostridium difficile infection and Clostridium difficile colitis*
Infusion site reactions	*phlebitis, infusion site erythema, infusion site induration, infusion site pain, infusion site phlebitis, vessel puncture site rash*
Peripheral edema	*Includes edema peripheral and peripheral swelling*
Central nervous system disorders	*slow speech, somnolence (neurologic), agitation, apathy, confusional state, delirium, disorientation (psychiatric)*
Hypertension	*Hypertension, blood pressure increased, and hypertensive crisis*
Anemia	*anemia, iron deficiency anemia, hemoglobin decreased*
Rash	*rash and rash generalized*
Pruritis	*pruritis and pruritis generalized*
Arrythmias	*atrial fibrillation and ventricular fibrillation*
Congestive cardiac failure	*cardiac failure chronic, cardiac failure congestive, diastolic dysfunction*

Significant Pooled AEs:

- Nausea (includes terms nausea and vomiting): 44 subjects total, 31 subjects (7.2%) in IMI/REL treatment group and 13 subjects (6.1%) in IMI plus Placebo treatment group

- Renal injury (includes terms blood creatinine increased, creatinine renal clearance decreased, acute kidney injury and renal impairment): 8 subjects total, 5 subjects (1.2%) in IMI/REL treatment group and 3 subjects (1.4%) in IMI plus Placebo treatment group.

- Thrombocytosis (includes thrombocytosis and platelet count increased): 15 subjects total, 12 subjects (2.8%) in IMI/REL treatment group and 3 subjects (1.4%) in IMI plus Placebo treatment group.

- *Clostridium difficile* infection (includes *Clostridium difficile* infection and *Clostridium difficile* colitis): 3 subjects total, 3 subjects (0.7%) in IMI/REL treatment group and 0 subjects in IMI plus Placebo treatment group.

- Infusion site reactions (includes phlebitis, infusion site erythema, infusion site induration, infusion site pain, infusion site phlebitis, vessel puncture site rash): 12 subjects total, 9 subjects (2.1%) in IMI/REL treatment group and 3 (1.4%) subjects in IMI plus Placebo treatment group.

- Central Nervous System Disorders (Neurological): includes slow speech, somnolence and Psychiatric: includes agitation, apathy, confusional state, delirium, disorientation): 7 subjects total, 2 subjects (0.5%) in IMI/REL treatment group and 5 subjects (2.3%) in IMI plus Placebo treatment group.

Table 64. Selected Treatment Emergent Adverse Events Occurring in ≥ 0.5% subjects of Studies PN003 and PN004

Treatment Emergent Adverse Events	IMI/REL any dose n=431	IMI/Placebo n=214	Total n=645
Nausea*	**31 (7.2%)**	**13 (6.1%)**	**44 (6.8%)**
Nausea	27 (6.3%)	12 (5.6%)	39 (6.0%)
Vomiting	17 (3.9%)	4 (1.9%)	21 (3.3%)
Diarrhea	**21 (4.9%)**	**9 (4.2%)**	**30 (4.7%)**
Headache	**14 (3.2%)**	**5 (2.3%)**	**19 (2.9%)**
Alanine aminotransferase increased	**13 (3.0%)**	**4 (1.9%)**	**17 (2.6%)**
Aspartate aminotransferase increased	**13 (3.0%)**	**3 (1.4%)**	**16 (2.5%)**
Hypertension*	**10 (2.3%)**	**6 (2.8%)**	**16 (2.5%)**
Hypertension	8 (1.9%)	5 (2.3%)	13 (2.0%)
Blood pressure increased	1 (0.2%)	1 (0.5%)	2 (0.3%)
Hypertensive crisis	1 (0.2%)	0 (0.0%)	1 (0.2%)
Thrombocytosis*	**12 (2.8%)**	**3 (1.4%)**	**15 (2.3%)**
Thrombocytosis	6 (1.4%)	2 (0.9%)	8 (1.2%)
Platelet count increased	6 (1.4%)	1 (0.5%)	7 (1.1%)
Infusion site reactions*	**9 (2.1%)**	**3 (1.4%)**	**12 (1.9%)**
Phlebitis	4 (0.9%)	3 (1.4%)	7 (1.1%)
Infusion site phlebitis	3 (0.7%)	0 (0.0%)	3 (0.5%)
Infusion site erythema	2 (0.5%)	0 (0.0%)	2 (0.3%)
Infusion site pain	1 (0.2%)	0 (0.0%)	1 (0.2%)
Infusion site induration	1 (0.2%)	0 (0.0%)	1 (0.2%)
Vessel puncture site rash	1 (0.2%)	0 (0.0%)	1 (0.2%)
Lipase increased*	**5 (1.2%)**	**4 (1.9%)**	**9 (1.4%)**
Anemia*	**5 (1.2%)**	**4 (1.9%)**	**9 (1.4%)**
Anemia	3 (0.7%)	3 (1.4%)	6 (0.9%)
Iron deficiency anemia	2 (0.5%)	0 (0.0%)	2 (0.3%)
Hemoglobin decreased	0 (0.0%)	1 (0.5%)	1 (0.2%)

Blood alkaline phosphatase increased	**6 (1.4%)**	**2 (0.9%)**	**8 (1.2%)**
Pyrexia	**5 (1.2%)**	**3 (1.4%)**	**8 (1.2%)**
Renal injury*	**5 (1.2%)**	**3 (1.4%)**	**8 (1.2%)**
Blood creatinine increased	2 (0.5%)	3 (1.4%)	5 (0.8%)
Creatinine renal clearance decreased	1 (0.2%)	0 (0.0%)	1 (0.2%)
Renal impairment	1 (0.2%)	0 (0.0%)	1 (0.2%)
Acute kidney injury	1 (0.2%)	0 (0.0%)	1 (0.2%)
Abdominal pain*	**6 (1.4%)**	**1 (0.5%)**	**7 (1.1%)**
Abdominal pain upper	3 (0.7%)	0 (0.0%)	3 (0.5%)
Abdominal pain	2 (0.5%)	0 (0.0%)	2 (0.3%)
Abdominal distension	0 (0.0%)	1 (0.5%)	1 (0.2%)
Abdominal discomfort	1 (0.2%)	0 (0.0%)	1 (0.2%)
Central Nervous System Disorders*	**2 (0.5%)**	**5 (2.3%)**	**7 (1.1%)**
Delirium	1 (0.2%)	2 (0.9%)	3 (0.5%)
Slow speech	0 (0.0%)	1 (0.5%)	1 (0.2%)
Somnolence	0 (0.0%)	1 (0.5%)	1 (0.2%)
Apathy	0 (0.0%)	1 (0.5%)	1 (0.2%)
Agitation	1 (0.2%)	0 (0.0%)	1 (0.2%)
Disorientation	0 (0.0%)	1 (0.5%)	1 (0.2%)
Confusional state	0 (0.0%)	1 (0.5%)	1 (0.2%)
Rash*	**4 (0.9%)**	**2 (0.9%)**	**6 (0.9%)**
Rash	4 (0.9%)	1 (0.5%)	5 (0.8%)
Rash generalised	0 (0.0%)	1 (0.5%)	1 (0.2%)
Peripheral edema*	**5 (1.2%)**	**1 (0.5%)**	**6 (0.9%)**
Oedema peripheral	5 (1.2%)	0 (0.0%)	5 (0.8%)
Peripheral swelling	0 (0.0%)	1 (0.5%)	1 (0.2%)
Arrythmias*	**4 (0.9%)**	**0 (0.0%)**	**4 (0.6%)**
Atrial fibrillation	4 (0.9%)	0 (0.0%)	4 (0.6%)
Ventricular fibrillation	1 (0.2%)	0 (0.0%)	1 (0.2%)
Back pain	**3 (0.7%)**	**1 (0.5%)**	**4 (0.6%)**
Protein urine present	**1 (0.2%)**	**3 (1.4%)**	**4 (0.6%)**
Protein urine present	1 (0.2%)	3 (1.4%)	4 (0.6%)
Constipation	**3 (0.7%)**	**1 (0.5%)**	**4 (0.6%)**
Dizziness	**2 (0.5%)**	**1 (0.5%)**	**3 (0.5%)**
Red blood cells urine positive	**1 (0.2%)**	**2 (0.9%)**	**3 (0.5%)**
Hyperkalaemia	**3 (0.7%)**	**0 (0.0%)**	**3 (0.5%)**
Neutrophil count increased	**1 (0.2%)**	**2 (0.9%)**	**3 (0.5%)**
Blood potassium decreased*	**1 (0.2%)**	**2 (0.9%)**	**3 (0.5%)**
Blood potassium decreased	1 (0.2%)	1 (0.5%)	2 (0.3%)
Hypokalaemia	0 (0.0%)	1 (0.5%)	1 (0.2%)
Pruritis*	**2 (0.5%)**	**1 (0.5%)**	**3 (0.5%)**
Pruritus	1 (0.2%)	1 (0.5%)	2 (0.3%)

Pruritus generalised	1 (0.2%)	0 (0.0%)	1 (0.2%)
Congestive cardiac failure*	**3 (0.7%)**	**0 (0.0%)**	**3 (0.5%)**
Cardiac failure congestive	2 (0.5%)	0 (0.0%)	2 (0.3%)
Cardiac failure chronic	1 (0.2%)	0 (0.0%)	1 (0.2%)
Diastolic dysfunction	1 (0.2%)	0 (0.0%)	1 (0.2%)
Clostridium difficile* infection	**3 (0.7%)**	**0 (0.0%)**	**3 (0.5%)**
Clostridium difficile colitis	2 (0.5%)	0 (0.0%)	2 (0.3%)
Clostridium difficile infection	1 (0.2%)	0 (0.0%)	1 (0.2%)
Blood phosphorus decreased*	**1 (0.2%)**	**2 (0.9%)**	**3 (0.5%)**
Blood phosphorus decreased	0 (0.0%)	2 (0.9%)	2 (0.3%)
Hypophosphataemia	1 (0.2%)	0 (0.0%)	1 (0.2%)

***Pooled AE term (see Table 63 for list of included individual dictionary derived or preferred terms)**

Reviewer Comment: Although minor differences are seen in the frequency of AEs of interest occurring in the IMI/REL treatment arms compared to the IMI arm, in general the differences were small and not clinically meaningful. Pooling of similar AE terms boosts the overall number of AEs under each category and this had implications for AE rates that will be reported in the labeling as AEs reported in ≥1% of subjects. For example, pooling of the following terms: blood creatinine increased, creatinine renal clearance decreased, renal impairment and acute kidney injury results in the pooled term "renal injury" occurring in a total of 8 subjects, with 5 subjects (1.2%) in the IMI/REL treatment group and 3 subjects (1.4%) in the IMI + Placebo treatment group. Similarly, pooling of infusion site reactions and phlebitis results in a total of 12 subjects, 9 subjects (2.1%) in the IMI/REL treatment group and 3 subjects (1.4%) in the IMI + Placebo treatment group. Central nervous system disorders (psychiatric and neurological) pooled together occurred in a total of 7 subjects, 2 subjects (0.5%) in IMI/REL treatment group and 5 subjects (2.3%) in IMI + Placebo treatment group. For the purpose of labeling we included AEs occurring in ≥1% of subjects and focused on the most relevant AEs in terms of known AE profile of IMI. These included GI disorders (nausea and diarrhea), liver transaminase and alkaline phosphatase elevations, lipase increases, infusion site reactions and pyrexia, headache and CNS adverse reactions, hypertension, anemia and renal injury.

Adverse reactions thought to have the greatest likelihood of relatedness to the study drug and occurring in greater than or equal to 1% of patients are listed in **Table 65**. This table lists each IMI/REL treatment group separately.

Table 65. Selected Adverse Reactions by System Organ Class Occurring in Greater Than or Equal to 1% of Subjects Receiving IMI/REL 250 mg or IMI in Studies PN003 and PN004

	IMI/REL 250mg (N=216) N (%)	IMI/Placebo (N=214) N (%)
Blood and lymphatic system disorders		
Anemia[a]	3 (1%)	4 (2%)

Gastrointestinal disorders		
Nausea	13 (6%)	13 (6%)
Vomiting	7 (3%)	4 (2%)
Diarrhea	12 (6%)	9 (4%)
Laboratory Investigations		
Alanine aminotransferase increased	7 (3%)	4 (2%)
Aspartate aminotransferase increased	6 (3%)	3 (1%)
Lipase increased	3 (1%)	4 (2%)
Blood creatinine increased	1 (<%)	3 (1%)
General disorders and administration site conditions		
Phlebitis/Infusion site reactions[b]	5 (2%)	3 (1%)
Pyrexia	5 (2%)	3 (1%)
Nervous system disorders		
Headache	9 (4%)	5 (2%)
Central Nervous System Reactions[c]	2 (1%)	5 (2%)
Vascular disorders		
Hypertension[d]	4 (2%)	6 (3%)

Source: Clinical Reviewer's Analysis

[a]*Anemia includes anemia and hemoglobin decreased*

[b]*Infusion site reactions include infusion site phlebitis, infusion site erythema, infusion site pain, infusion site induration, vessel puncture site rash*

[c]*Central nervous system reactions include agitation, apathy, confusional state, delirium, disorientation, slow speech, and somnolence*

[d]*Hypertension includes hypertension and blood pressure increased*

*Reviewer comment: **Table 65** details the most relevant selected AEs in PN003 and PN004 based on known AEs associated with IMI, as well as animal data showing CNS toxicity and renal injury associated with relebactam. Pooling of related terms for possibly related AEs was important to establish a more robust analysis of the frequency data. **Table 65** also comprises the list of AEs represented in the proposed label for IMI/REL based on the Agency's analysis. Overall, the rates of adverse reactions were similar in IMI/REL 125 mg, IMI/REL 250 mg, and IMI/Placebo groups.*

Study PN013

Randomized Treatment Arms

In the randomized arms of PN013, reactions occurred in 71% (22/31) of patients receiving IMI/REL as compared to 81.3% (13/16) of patients receiving colistin plus IMI. Certain similar adverse events were pooled together by the Agency to allow for more accurate and robust analysis. **Table 66** includes a list of pooled AE terms and the preferred MedDRA terms included under each pooled term. Adverse reactions that occurred in at least 1 subject in the randomized arms of Study PN013 are presented in Table 67.

Table 66. Pooled Adverse Events by Related Preferred Terms for Trial PN013

Pooled AE Term	**Preferred MedDRA Terms**
Nausea	*Includes nausea and vomiting*
Renal injury	*Includes blood creatinine increased, creatinine renal clearance decreased, glomerular filtration rate decreased, blood urea increased, renal failure*
Hemoglobin decreased	*Includes hemoglobin decreased and anemia*
Infusion site reactions	*Includes infusion site erythema, infusion site hematoma and infusion site phlebitis*
Gastroesophageal disorders	*Includes gastroesophageal reflux disease, gastritis, and dyspepsia*
Arrythmias	*Includes atrial fibrillation, atrial flutter, supraventricular extrasystoles, tachyarrhythmia, ventricular tachycardia*
White blood cell count decreased	*Includes leukopenia and white blood cell count decreased*
Mental status changes	*Includes mental status changes, delirium, agitation*

Table 67. Adverse Reactions Occurring in at Least 1 Subject in the Randomized Arms of PN013

System Organ Class	MedDRA Preferred Term	**IMI/REL* N=31 n (%)**	**Colistin + IMI† N=16 n (%)**
Investigations	Aspartate aminotransferase increased	3 (9.7%)	3 (18.8%)
	Alanine aminotransferase increased	2 (6.5%)	3 (18.8%)
	Liver function test increased	0 (0.0%)	1 (6.3%)

	Blood alkaline phosphatase increased	1 (3.2%)	2 (12.5%)
	Gamma-glutamyltransferase increased	1 (3.2%)	2 (12.5%)
General disorders and administration site conditions	Pyrexia	4 (12.9%)	2 (12.5%)
	Infusion site reactions[a]	3 (9.7%)	2 (12.5%)
Gastrointestinal disorders	Nausea[b]	3 (9.7%)	4 (25%)
	Gastrooesophageal disorders[c]	1 (3.2%)	2 (12.5%)
	Hypoaesthesia oral	0 (0.0%)	2 (12.5%)
	Constipation	1 (3.2%)	0 (0.0%)
Blood and lymphatic disorders/Investigations	Hemoglobin decreased[d]	3 (9.7%)	2 (12.5%)
	White blood cell count decreased[e]	1 (3.2%)	1 (6.3%)
Renal and urinary disorders/Investigations	Creatinine change/renal injury[f]	3 (9.7%)	8 (50%)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	3 (9.7%)	0 (0.0%)
	Epistaxis	0 (0.0%)	1 (6.3%)
Nervous System disorders	Dizziness	0 (0.0%)	2 (12.5%)
Cardiac disorders	Arrythmias[g]	2 (6.5%)	2 (12.5%)
Hepatobiliary disorders	Hepatic failure	0 (0.0%)	1 (6.3%)
Metabolism and nutrition disorders	Hyperglycaemia	1 (3.2%)	0 (0.0%)
Psychiatric disorders	Mental status changes	1 (3.2%)	1 (6.3%)

IMI/RELTRADEMARK 1.25 g (500 mg imipenem/500 mg cilastatin/250 mg relebactam) IV every 6 hours.

[†]*Colistin provided as colistimethate sodium (loading dose of 300 mg colistin base activity (CBA) followed by 150 mg CBA (corresponding to ~360 mg colistimethate sodium or ~4.5 million IU) IV every 12 hours) + imipenem/cilastatin (500 mg/500 mg, IV every 6 hours).*

[a]*Includes infusion site erythema, infusion site hematoma and infusion site phlebitis*

[b]*Includes nausea and vomiting*

[c]*Includes gastroesophageal reflux disease, gastritis, and dyspepsia*

[d]*Includes hemoglobin decreased and anemia*

[e]*Includes leukopenia and white blood cell count decreased*

[f]*Includes blood creatinine increased, creatinine renal clearance decreased, glomerular filtration rate decreased, blood urea increased, renal failure*

[g]*Includes atrial fibrillation, atrial flutter, supraventricular extrasystoles, tachyarrhythmia, ventricular tachycardia*

Reviewer Comment: There were more AEs reported in the comparator arm (Treatment Group 2: CMS + IMI) compared to the study drug arm (Treatment Group 1: IMI/REL). This is consistent with the labeled toxicities associated with colistin, particularly renal toxicity. The sample size of this study was small, however the AEs observed with IMI/REL in the randomized treatment arms of PN013 were similar to those observed in PN003 and PN004 except for diarrhea which was more frequently reported in latter two trials. The most frequently reported AEs in the IMI/REL arm included in descending order, pyrexia, infusion site reactions, nausea, AST increase, hemoglobin decrease, renal injury, dyspnea, ALT increase, and arrythmias.

Open-label Treatment Arm

Adverse reactions that occurred in the open label arm of PN013, where all subjects received IMI/REL 250 mg, are presented in Table 68.

Table 68. Adverse Reactions Occurring in at Least 1 Subject in the Open Label Arm of Study PN013

System Organ Class	MedDRA Preferred Term	IMI/REL 250mg* N=3 N (%)
Renal and urinary disorders	Acute kidney injury	1 (33.3%)
Blood and lymphatic system disorders	Anemia	1 (33.3%)
Cardiac disorders	Atrial flutter	1 (33.3%)
Gastrointestinal disorders	Constipation	1 (33.3%)
	Gastroesophageal reflux disease	1 (33.3%)
	Ileus	1 (33.3%)
	Retching	1 (33.3%)
Metabolism and nutrition disorders	Decreased appetite	1 (33.3%)
Gastrointestinal disorders	Diarrhea	1 (33.3%)
Nervous system disorders	Generalized tonic-clonic seizure	1 (33.3%)
Metabolism and nutrition disorders	Hyperkalemia	1 (33.3%)
	Hypomagnesaemia	1 (33.3%)
Psychiatric disorders	Mental status changes	1 (33.3%)

**IMI/REL 1.25 g (500 mg imipenem/500 mg cilastatin/250 mg relebactam) IV every 6 hours.*

Reviewer Comment: The most significant AE occurring in the open-label arm of the trial was one case of generalized tonic-clonic seizure, which was the only case of seizure seen across all the

clinical studies. Seizure is a labeled AE associated with IMI. The incidence of seizure is lower than that observed in other studies with IMI, however given the small sample size of these studies, caution must be used not to interpet a protective effect of REL. It was noted by the Applicant that the patient who experienced the seizure inadvertently received a non-study dose of IMI, although it is difficult to ascertain whether the inadvertent single extra dose was the specific cause of the seizure in this patient. Labeling for IMI/REL is planned to include seizures as a warning.

Laboratory Findings

Phase 1 Trials

There were no changes from baseline observed for hematology and chemistry laboratory parameter in the seven Phase 1 trials apart from liver transaminase elevations. Liver transaminase elevations were observed following administration of multiple doses of REL in P001 and P012. All subjects with elevated liver transaminases were asymptomatic. Details on liver transaminase elevations in the development program for IMI/REL, including the Phase 1, 2 and 3 trials, can be found in Section 7.4.5 Analysis of Submission-Specific Safety Issues.

PN003 and PN004

Laboratory data were integrated for PN003 and PN004. The following laboratory parameters were evaluated:

- Hematology
    - WBC, Eosinophils, Hemoglobin, Hematocrit, Leukocytes, Platelets

- Chemistry
    - AST, ALT, Alkaline Phosphatase, Total bilirubin, Direct bilirubin, Indirect bilirubin, BUN, Creatinine, Glucose, Sodium, Potassium

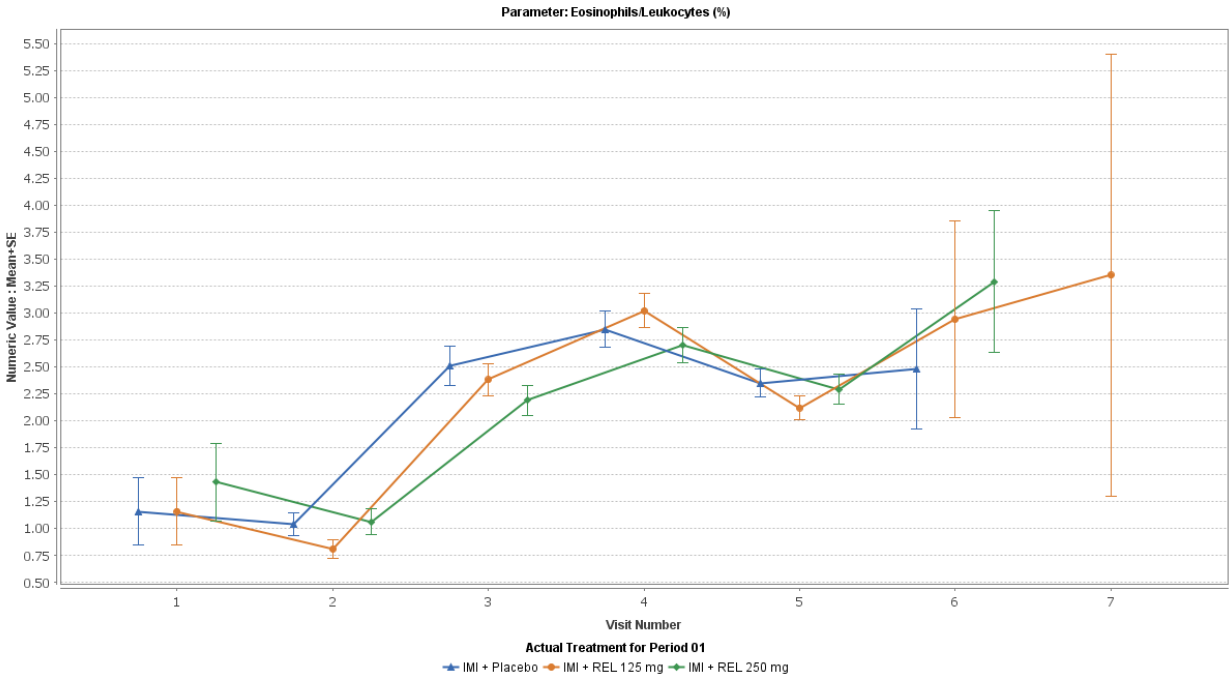
Differences between the mean values calculated per laboratory parameter were compared across visits and between treatment groups. With the exception of occasional outliers and minor non-clinically meaningful differences, no significant changes from baseline across visits or between groups was noted for the majority of the mean laboratory parameters analyzed. Laboratory test abnormalities that were noted to be adverse events or significant deviations from normal values for individual subjects are discussed elsewhere. Trends towards differences were noted for the following laboratory parameters:

Eosinophils

The overall mean ranges for eosinophils (%) remained within normal levels across visits and treatment groups, however there was a noticeable trending up from the screening visit (Visit 1)

to the Late Follow-Up (LFU: Visit 7) across all treatment groups with an increase in the mean eosinophil percent from a range of 1.0-1.5% at the screening visit to 2.25-3.25% at the last available visit recorded (Figure 1).

Figure 1. Mean Eosinophils (%) Across Visits and Treatment Groups PN003 and PN004



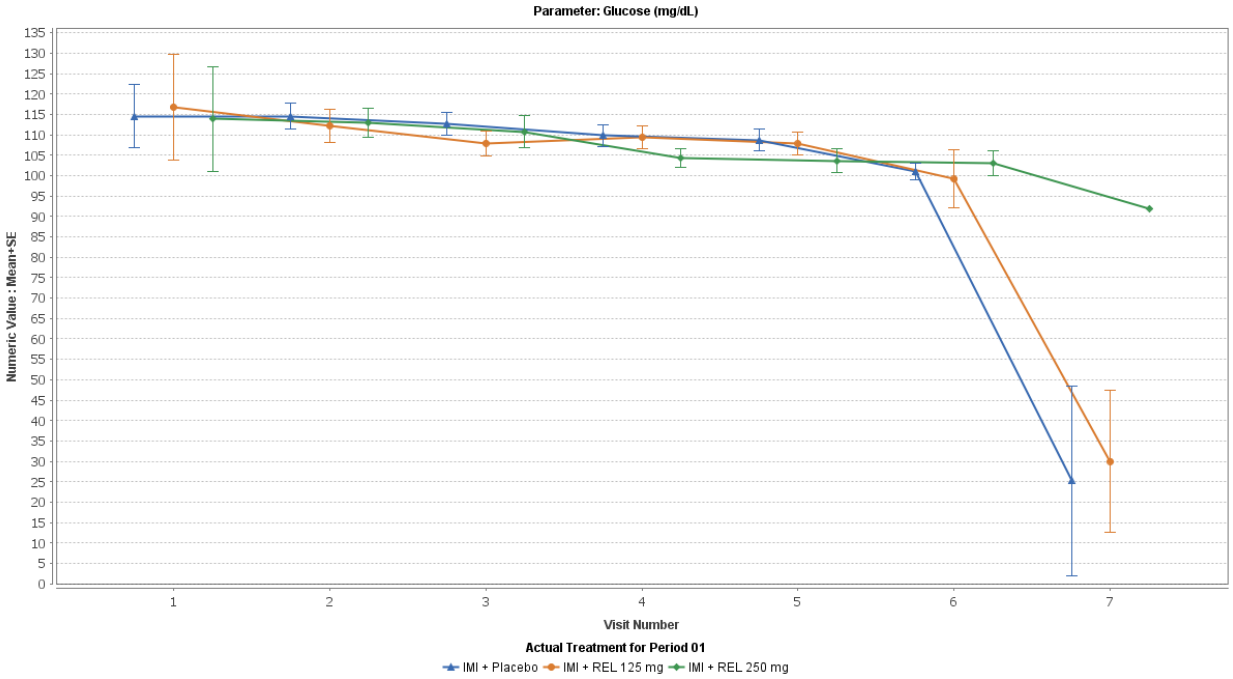
**Visit 1=Screening; Visit 2=Randomization; Visit 3=IV; Visit 4=DCIV; Visit 5=EFU; Visit 6=GFU; Visit 7=LFU*

Reviewer comment: Increased eosinophils are mentioned as an adverse laboratory change in the IMI label. The mechanism of this increase in eosinophils is not clear. This finding did not emerge in the analysis of reported adverse events and because the trend noted here is minimal without any clear difference between the different treatment groups, it is not planned to be included in the label for IMI/REL.

Glucose

Mean glucose levels remain within normal levels without significant variation from baseline from Visits 1 through 6 with a significant drop to very low levels in both the IMI + Placebo group and IMI + REL 125mg treatment group at Visit 7. Mean glucose levels remained unchanged in the IMI + REL 250mg treatment group (Figure 2).

Figure 2. Mean Glucose (mg/dL) Across Visits and Treatment Groups in PN003 and PN004



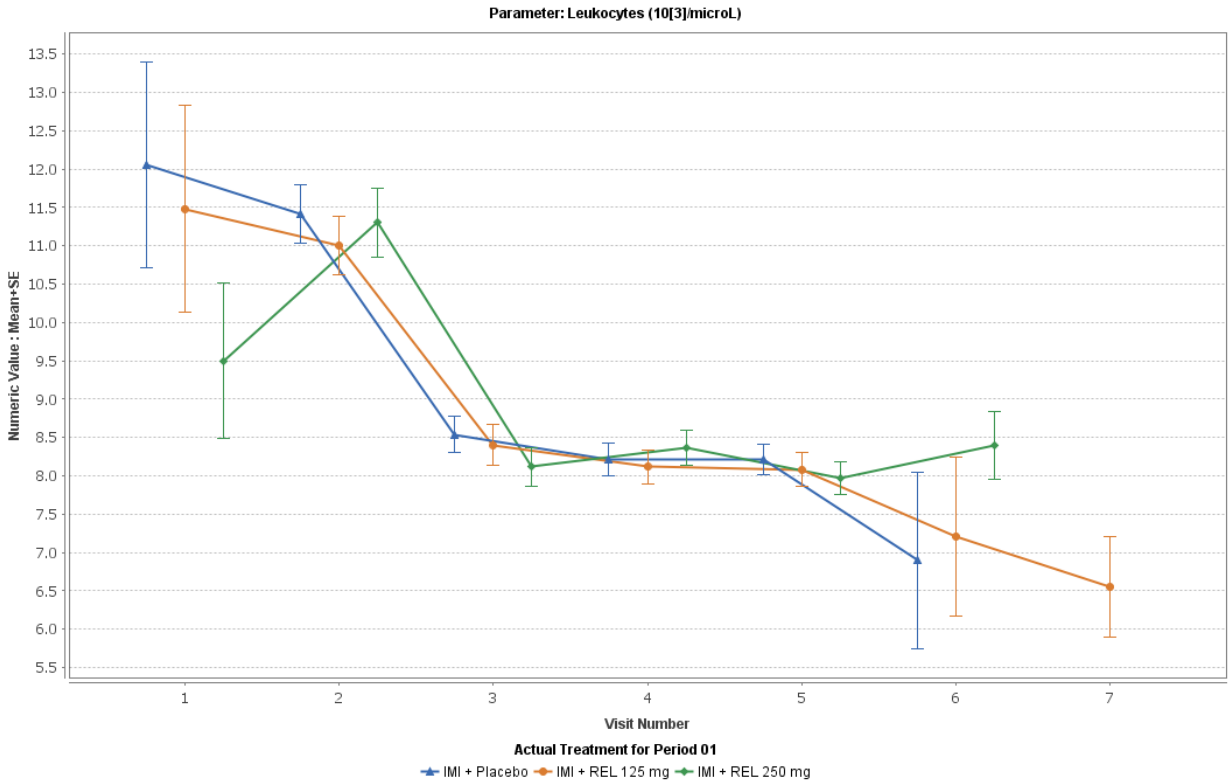
**Visit 1=Screening; Visit 2=Randomization; Visit 3=IV; Visit 4=DCIV; Visit 5=EFU; Visit 6=GFU; Visit 7=LFU*

Reviewer Comment: The mean glucose levels of 25 mg/dL (s.e. 23) in the IMI + Placebo treatment group and 30 mg/dL (s.e. 17) in the IMI + REL 125mg treatment group reported at the LFU visit are likely outliers skewed by the presence of a few low numbers in the presence of an overall small sample size. This assumption is supported by the large standard error. Additionally, it is difficult to interpret these numbers at a single visit in the context of study drug having been discontinued for several subjects by this point in the trial.

Leukocytes

Mean leukocytes (10^3/µL) are noted to downtrend from Visit 1 to Visit 7 across all treatment groups, from a mean of 9-12 x 10^3/µL at the screening visit (Visit 1) to a mean of 6.6-8.4 x 10^3/µL at the last available visit (Visit 6 and/or 7) (Figure 3).

Figure 3. Mean Leukocytes (10^3/µL) Across Visits and Treatment Groups in Studies PN003 and PN004

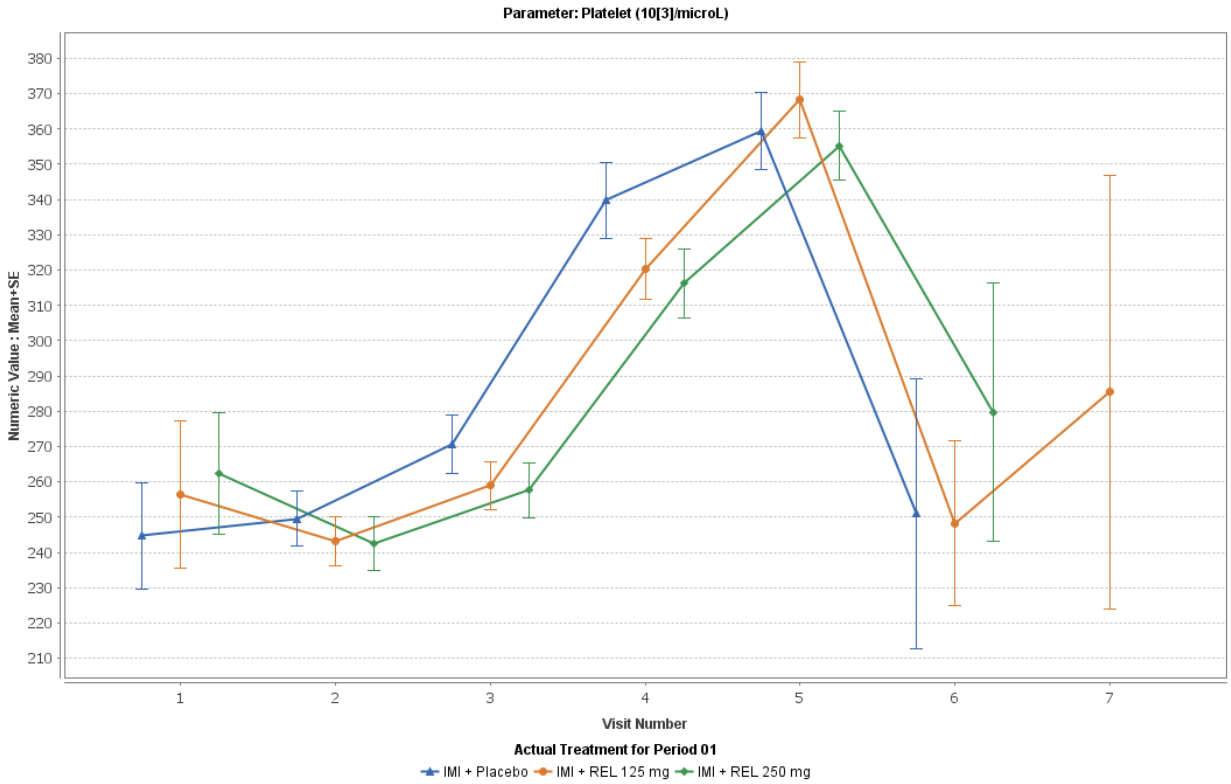


Reviewer Comment: The downtrending of leukocytes noted here is consistent with leukopenia described as an adverse event with administration of both IMI and IMI/REL. It is also consistent with improvement in infection.

Platelets

Mean platelet values are noted to increase from Visit 1 to Visit 5 but then decrease quickly back to baseline or near baseline values across all treatment groups.

Figure 4. Mean Platelets (10^3/µL) Across Visits and Treatment Groups in Studies PN003 and PN004



Reviewer Comment: Thrombocytosis is also cited in the imipenem label. The mechanism is unclear. This was considered in the labeling approach for IMI/REL as well, but ultimately not included as the overall numbers reported of thrombocytosis reported were low.

In general, in PN003 and PN004 there were no major differences noted in laboratory value trends between IMI/REL and IMI. For both IMI/REL and IMI, there were slight increases in eosinophils and platelets noted following study drug administration, a trend toward decreases in glucose towards visit 7, as well as decreases in leukocytes (likely consistent with improvement in infection).

PN013

Laboratory data was not integrated between PN013 and PN003/PN004. Laboratory data from PN013 were thus analyzed separately. Similar to PN003 and PN004, the following laboratory parameters were evaluated for changes in PN013:

- Hematology
    - WBC, Eosinophils, Hemoglobin, Hematocrit, Leukocytes, Platelets

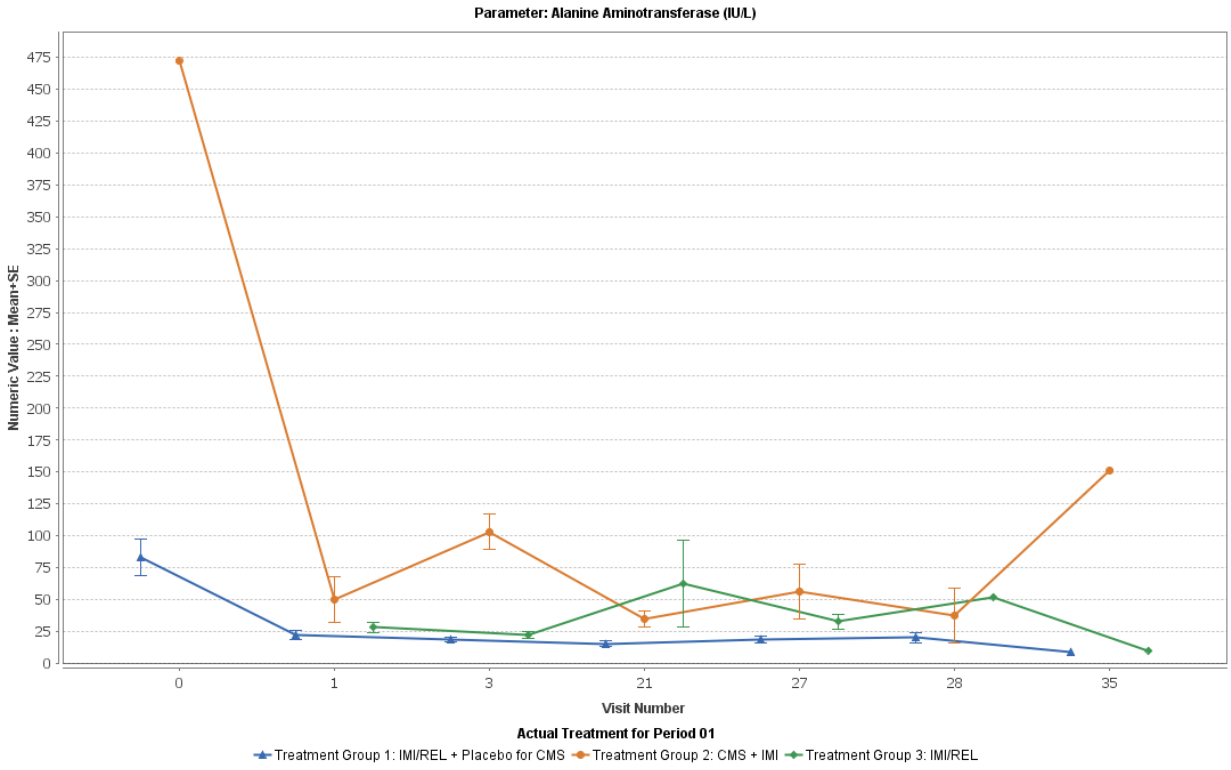
- Chemistry
    - AST, ALT, Alkaline Phosphatase, Total bilirubin, Direct bilirubin, Indirect bilirubin, BUN, Creatinine, Glucose, Sodium, Potassium

Differences between the mean values calculated per laboratory parameter were compared across visits and between treatment groups.

ALT

Mean ALT values at the screening visit were higher in Treatment Group 2, CMS plus IMI, (472 IU/L, s.e. 0) compared to Treatment Group 1, IMI/REL plus placebo for CMS, (83 IU/L, s.e. 14), Figure 5. Mean values at the remainder of the visits were comparable between treatment groups.

Figure 5. Mean ALT (IU/L) Across Visits and Treatment Groups in PN013



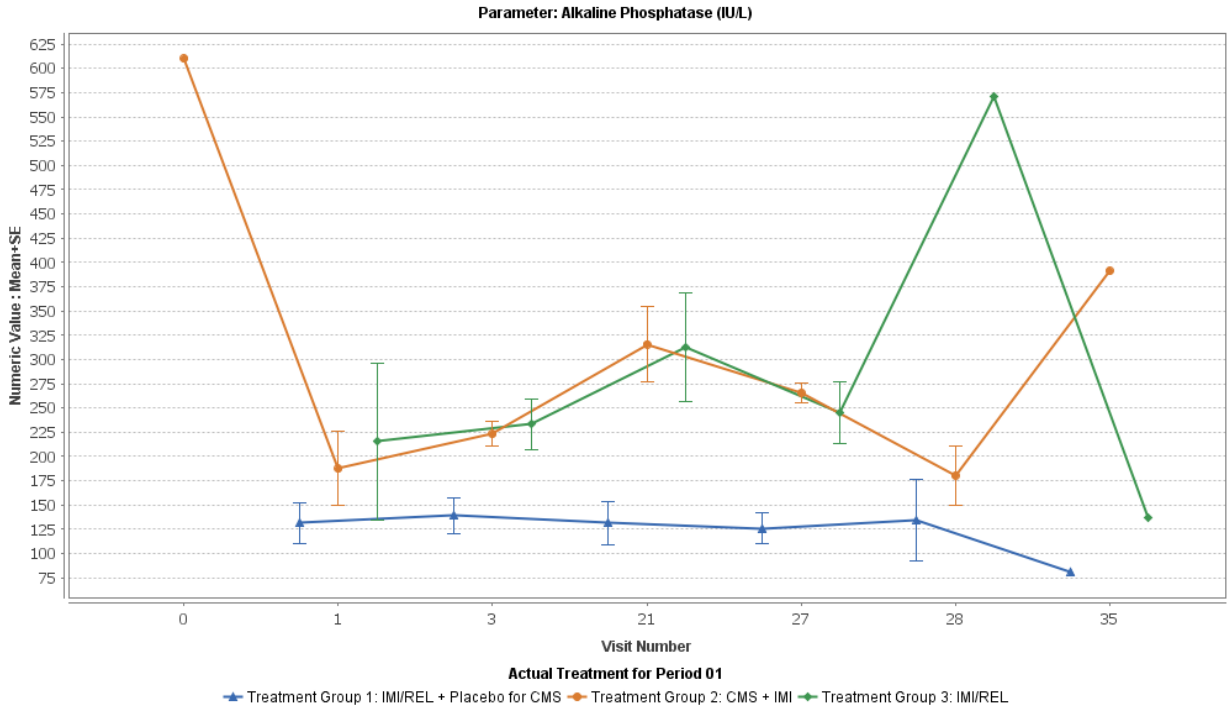
Reviewer Comment: Outlier value of AST 472 IU/L at the screening visit in Treatment Group 2 is likely due to the very small number of patients in this trial and treatment arm.

Alkaline Phosphatase

Mean alkaline phosphatase values, similarly to ALT values were also noted to be significantly

higher at the screening visit in Treatment Group 2, CMS plus IMI, (610 IU/L, s.e. 0) compared to Treatment Group 1, IMI/REL plus placebo for CMS, (131 IU/L, s.e. 21) (Figure 6). This is likely due to the small numbers included, especially at the screening visit. Alkaline phosphatase remained slightly elevated in Treatment Group 2 compared to Treatment Group 1 across all visits. Treatment Group 3, IMI/REL open-label arm, is displayed in the figure below, was not considered for purposes of analysis due to the small sample size (n=3) in this open-label treatment arm.

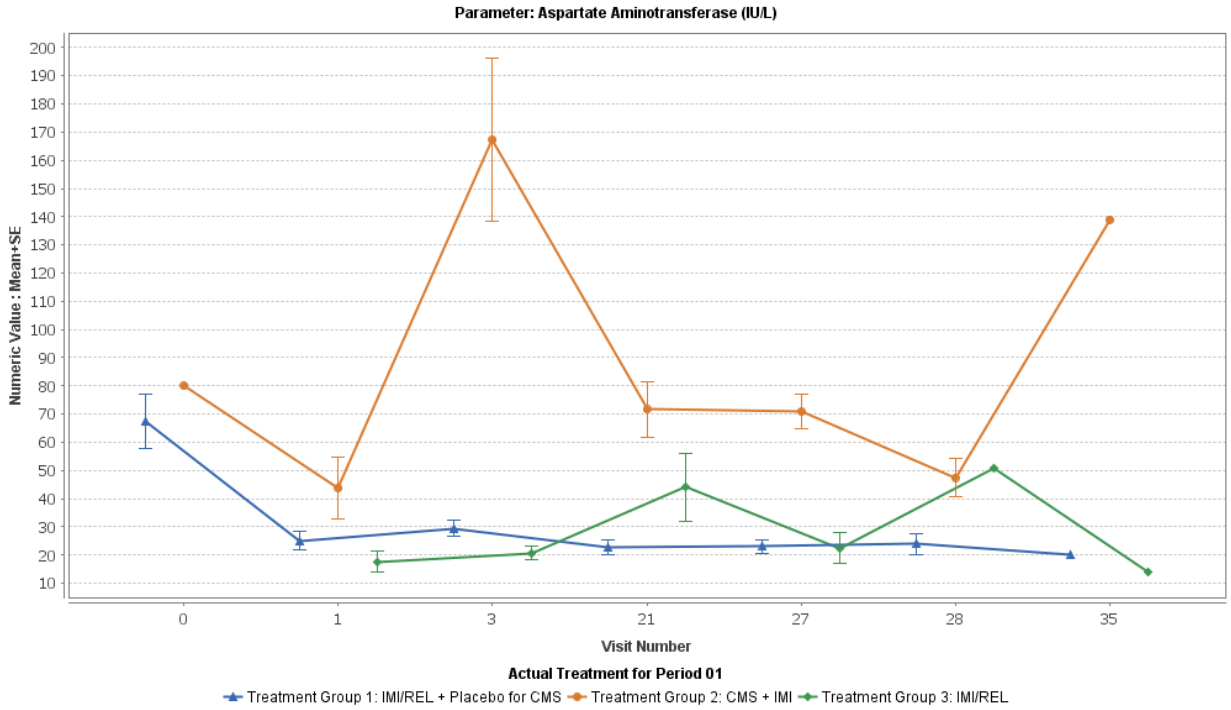
Figure 6. Mean Alkaline Phosphatase (IU/L) Across Visits and Treatment Groups in PN013



AST

Mean AST values were noted to be slightly higher in Treatment Group 2, CMS plus IMI, compared to Treatment Group 1, IMI/REL plus placebo for CMS, with the difference particularly notable at Visit 3 and at end of follow up (day 35), Figure 7.

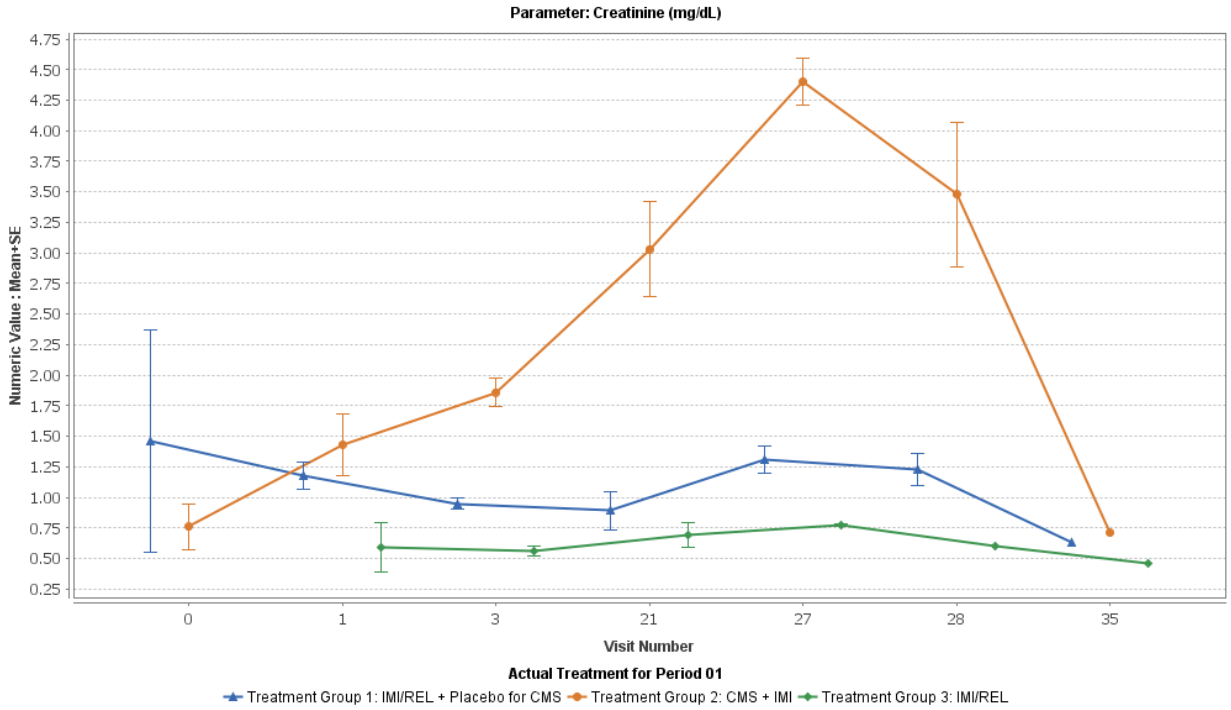
Figure 7. Mean AST (IU/L) Across Visits and Treatment Groups in PN013



Creatinine

Mean creatinine was the most significant difference noted between the two randomized treatment groups in Study PN013, with a steady increase in mean creatinine noted in Treatment Group 2, CMS plus IMI, from a baseline of 0.76 mg/dL (s.e. 0.19) to a peak of 4.4 (s.e. 0.19) at day 27 compared to a baseline of 1.46 mg/dL in Treatment Group 1, IMI/REL plus placebo for CMS, with a slight decline thereafter (Figure 8).

Figure 8. Mean Creatinine (mg/dL) Across Visits and Treatment Groups in Study PN013



Reviewer Comment: Increased nephrotoxicity with colistin is an expected adverse effect of this drug and the differences between the two treatment groups are consistent with recognized nephrotoxic adverse event rates of the drugs in both treatment arms.

Overall, there were more abnormal laboratory values noted in PN013 compared to PN003 and PN004, consistent with the increased morbidity of patients enrolled in PN013. The largest difference between the randomized treatment groups, Treatment Group 1 (IMI/REL plus Placebo to CMS) and Treatment Group 2 CMS plus IMI) were seen in differences in mean creatinine values reported across visits. There were also some differences noted in liver transaminase values with higher mean ALT, AST and alkaline phosphatase values in Treatment Group 2. Laboratory test abnormalities that were noted to be adverse events or significant deviations from normal values for individual subjects are discussed under the adverse events section.

Vital Signs

Vital sign measurements were not integrated across PN003 and PN004 are presented below separately for each study and for study PN013.

Study PN003

In general, vital sign measurements across the three treatment groups in Study PN003 were

comparable. There was some minor variability seen in the following vital signs across treatment groups: systolic blood pressure (SBP), temperature, and respiratory rate (RR). Mean SBP across visits ranged from a low of 110mmHg to a high of 156mmHg. Highest temperature values recorded across visits included a mean of 37.9˚C and a mean of 38.3˚C. Lowest temperature recorded was 36˚C. Highest mean respiratory rate recorded was at the upper limit of normal at 20 breaths/minute.

Reviewer Comment: The highest SBP values were recorded in subjects in the IMI/REL 250mg treatment group, however the differences between treatment groups are not clinically meaningful. The highest and lowest temperature values were recorded in subjects also in the IMI/REL 250mg treatment group, however the range of values is not outside that expected for subjects presenting with infection and the differences between treatment groups were also not clinically meaningful. Mean respiratory rate was also highest in subjects in the IMI/REL 250mg treatment group, however the recorded values were within the expected normal range.

Study PN004

Vital signs across the three treatment groups in Study PN004 were comparable. No significant differences were seen between the treatment groups in mean systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, or pulse rate, across visits. Mean RR was also comparable across all groups with the exception of one outlier at one visit point with a mean RR of 26 in the Placebo + IMI treatment group.

Reviewer Comment: Minor differences seen in respiratory rate across treatment group were not clinically meaningful.

Study PN013

Vital signs across the two randomized treatment groups in Study PN013 were comparable with no relevant or clinically meaningful differences in mean SBP, DBP, RR, pulse rate or temperature to note.

Vital signs for the open-label, nonrandomized Treatment Group 3 were not compared to the other groups as the number of subjects (n=3) was too small to allow meaningful analysis.

Reviewer Comment: Vital signs measurements across all treatment groups in PN003, PN004 and PN013 were comparable. There was some minor variability seen in SBP, temperature, and RR in PN003 and in respiratory rate in PN004 that were not clinically meaningful.

Electrocardiograms (ECGs)

ECG assessments were not performed in PN003, PN004 or PN013. A dedicated Phase 1 trial to evaluate QT interval was conducted and is discussed in the QT section below.

QT Evaluation

A Phase 1 trial (P009) was conducted to evaluate the effect of REL on QTc intervals. A QT studies consultation review was requested from the QT Interdisciplinary Review Team (QT-IRT). The P009 study was analyzed by the QT-IRT using central tendency as the primary analysis. REL was administered at a supratherapeutic dose of 1150mg and compared to negative and positive controls, including moxifloxacin. There was no statistically significant change in QTc intervals following administration of REL in this trial. Other ECG parameters including PR and RR intervals, QRS duration, T-wave morphology, and the presence of U-waves were all assessed without any evidence of significant changes. The QT-IRT team proposed edits to the label, which are discussed in Section 10 Labeling .

Immunogenicity

No immunogenicity/antigenicity evaluations were conducted as part of this development program.

7.4.5 Analysis of Submission-Specific Safety Issues

Liver Transaminase Elevations

Study PN003 (cUTI)

There were no cases of Hy's Law observed in PN003. Five subjects had AST and ALT elevations ≥ 3x and/or 5x ULN in the IMI/REL treatment groups (IMI/REL 125mg and IMI/REL 250mg) but not in the IMI + Placebo treatment group. Evidence of cholestasis with total bilirubin > 1.5x ULN was observed in the IMI/REL treatment group only (IMI/REL 250mg) (Figure 9 and Figure 10).

- AST/ALT ≥ 3x ULN, Tbili ≥ 2x ULN and ALP < 2x ULN
  - 0 subjects

- AST/ALT ≥ 5x ULN
  - 2 subjects (1 subject IMI/REL 125mg, 1 subject IMI/REL 250mg)

- AST/ALT ≥ 3x ULN
  - 5 subjects (3 subjects IMI/REL 125mg)

Figure 9. Elevations of Aspartate Aminotransferase (AST) and Total Bilirubin Among Subjects Receiving IMI/REL or IMI + Placebo in PN003

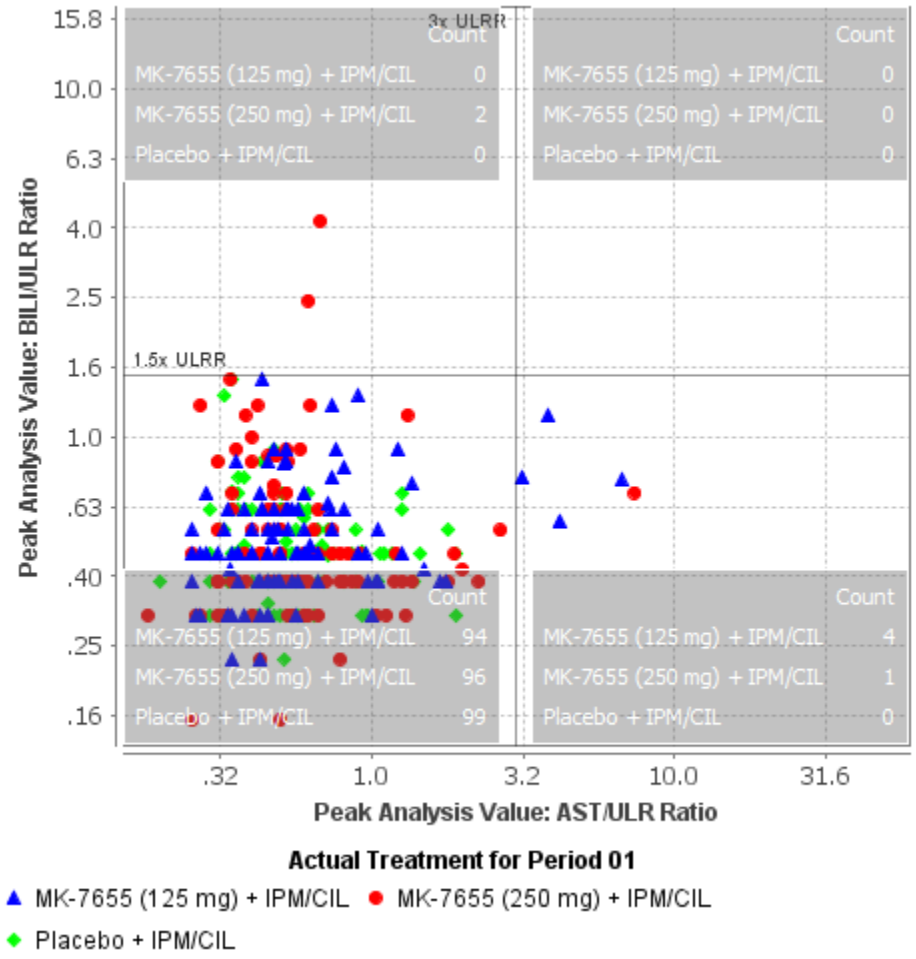
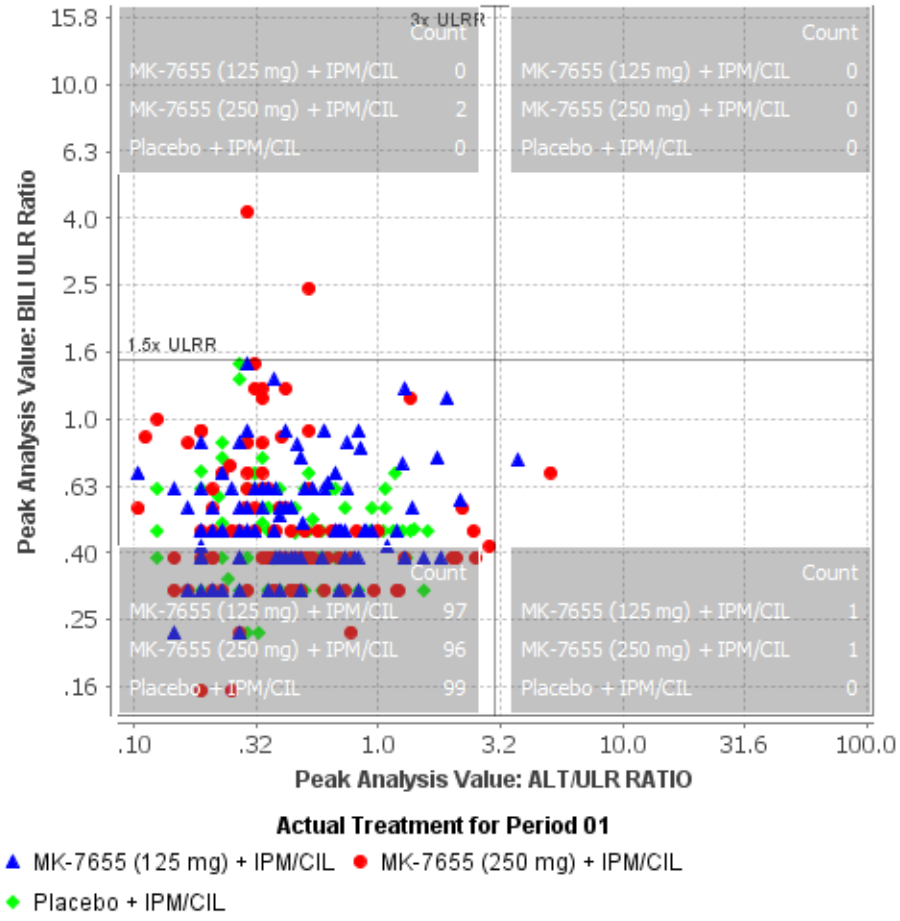


Figure 10. Elevations of Alanine Aminotransferase (ALT) and Total Bilirubin Among Subjects Receiving IMI/REL or IMI + Placebo in PN003



Study PN004 (cIAI)

There was one subject meeting laboratory criteria for Hy's Law in the IMI/REL 250mg treatment group of Study PN004, however due to baseline elevation of total bilirubin >3x ULN, this patient was not considered a true Hy's Law case. This subject's narrative is presented below:

- 77-year-old white male receiving IMI + REL 250mg. The patient was diagnosed with cholelithiasis and septic shock on 3 April and underwent exploratory laparotomy and subtotal gastric resection for acute gastric perforation/peptic ulcer. The patient was started on the study drug one day later on 4 April. On baseline laboratory studies, the patient had a normal AST and ALT and a total bilirubin > 3x ULN. On day 2 of study drug treatment (5 April), he was noted to have rising transaminases:
    - ALT 248 IU/L (6.9x ULN)
    - AST 430 IU/L (11.3 x ULN)
    - Total bilirubin 3.3 mg/dL (3.3x ULN)

  Study treatment was not discontinued, and he completed study drug on day 8 (11 April).

AST and ALT also returned to baseline. Study investigator deemed the noted transaminase elevations as unrelated to study drug.

Reviewer Comment: The timing of the patient's surgery and acute abdominal catastrophe was a confounding factor and it is difficult to ascertain whether the liver transaminase elevations (AST and ALT) were due to the abdominal injury and ensuing post-surgical course or related to the study drug. The resolution of the transaminase elevation despite continuation of the study treatment supports the former being the etiology of the transaminitis.

Fourteen subjects had AST and ALT elevations ≥ 3x ULN in PN004, 5 subjects in the IMI/REL 125mg treatment group, 6 subjects in the IMI/REL 250mg treatment group and 3 subjects in the IMI + Placebo treatment group. Evidence of cholestasis with total bilirubin > 1.5x ULN was observed across all treatment groups, 10 subjects each in the IMI/REL 125mg and IMI/REL 250mg treatment groups and 7 subjects in the IMI + Placebo Treatment Groups (Figure 11 and Figure 12).

- AST/ALT ≥ 3x ULN, Tbili ≥ 2x ULN and ALP < 2x ULN
  - 1 subject (narrative above)

- AST/ALT ≥ 5x ULN
  - 9 subjects (3 subjects IMI/REL 125mg, 4 subjects IMI/REL 250mg, 2 subjects IMI + Placebo)

- AST/ALT ≥ 3x and < 5xULN
  - 14 subjects (5 subjects IMI/REL 125mg, 6 subjects IMI/REL 250mg, 3 subject IMI + Placebo)

Reviewer Comment: The greater number of total bilirubin elevations ≥ 1.5x ULN is likely due to the nature of the infections enrolled in this study, complicated intrabdominal infections, with associated liver/biliary injury leading to increased bilirubin elevations compared to the cUTI trial (PN003). The transaminase elevations may also be due to the study drug as they were also noted in the cUTI study and the Phase 1 trials.

Figure 11. Elevations of Aspartate Aminotransferase (AST) and Total Bilirubin Among Subjects Receiving IMI/REL or IMI + Placebo in PN004

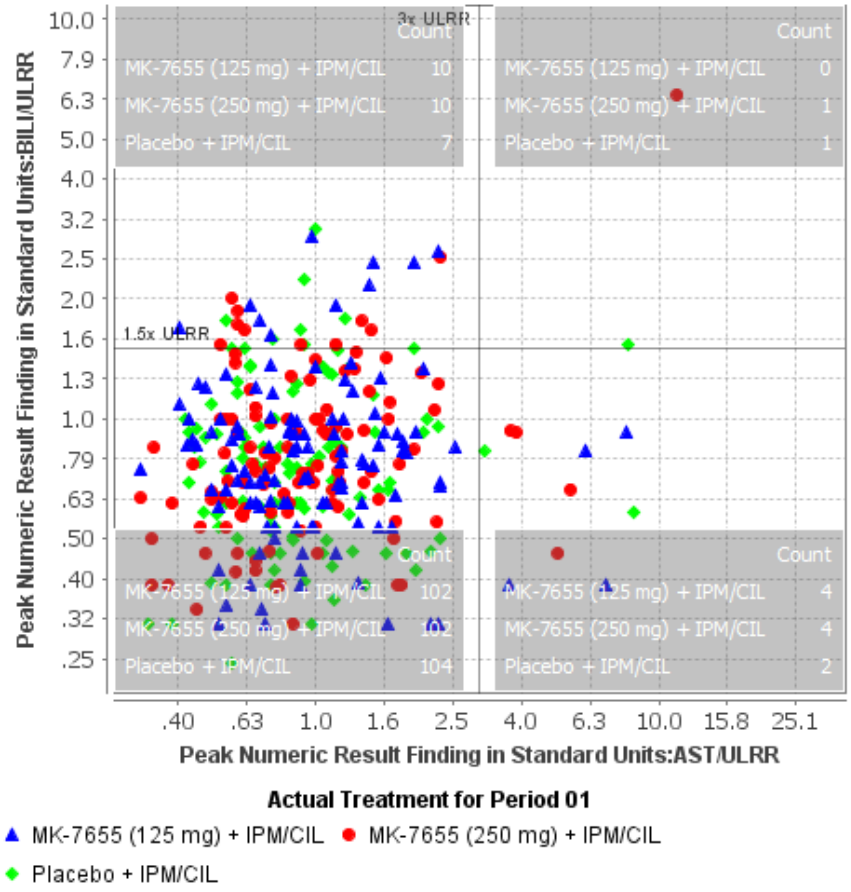
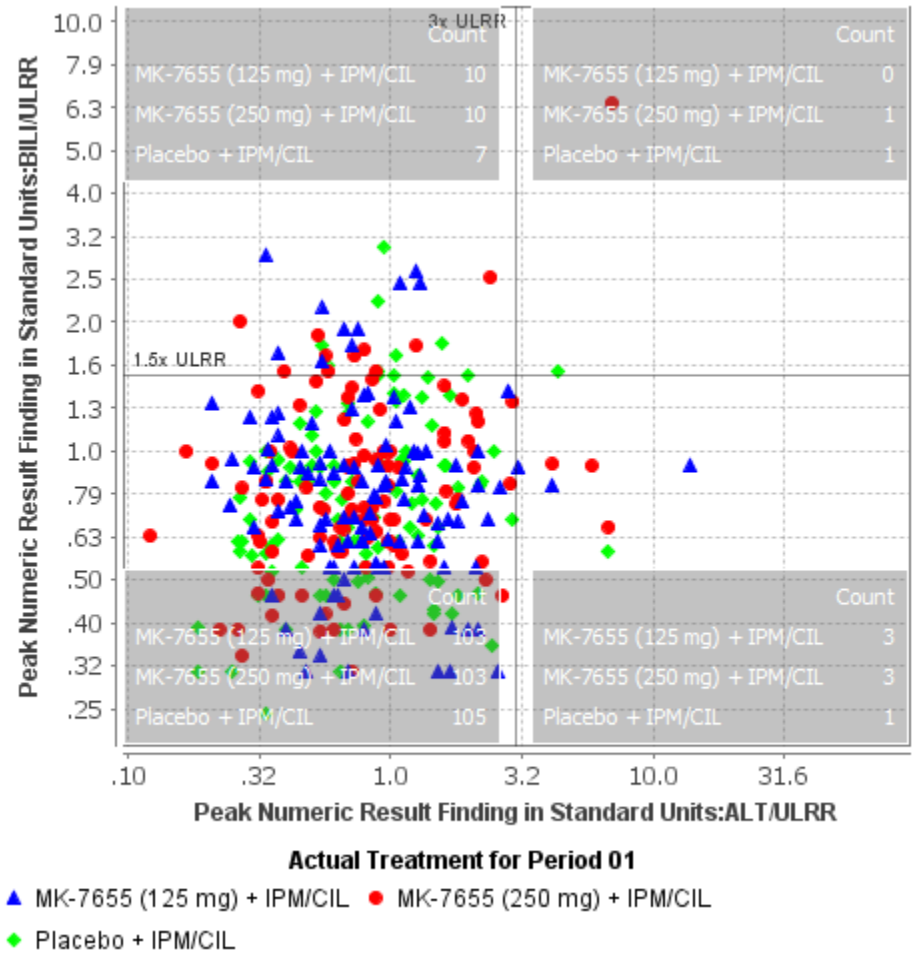


Figure 12. Elevations of Alanine Aminotransferase (ALT) and Total Bilirubin Among Subjects Receiving IMI/REL or IMI + Placebo in PN004



Study PN013

There were two potential cases of Hy's Law observed in Study PN013, however both cases were in the comparator treatment group receiving CMS plus IMI. No cases of Hy's Law were observed in subjects receiving IMI/REL.

There were 6 subjects with AST and AST ≥ 3x ULN in the Study PN013, all of which were in Treatment Group 2 (CMS plus IMI), with the exception of one subject in Treatment Group 1 (IMI/REL plus Placebo to CMS) (Figure 13). Evidence of cholestasis with total bilirubin > 1.5x ULN was observed in 3 subjects in Treatment Group 2 (CMS plus IMI) and 1 subject in Treatment Group 1 (IMI/REL plus Placebo to CMS) (Figure 14).

- AST/ALT ≥ 3x ULN, Tbili ≥ 2x ULN and ALP < 2x ULN
    - 2 subjects (Treatment Group 2: CMS plus IMI)

- AST/ALT ≥ 5x ULN
  - 3 subjects (Treatment Group 2: CMS plus IMI)

- AST/ALT ≥ 3x ULN
  - 6 subjects (1 subject Treatment Group 1: IMI plus Placebo to CMS, 5 subjects Treatment Group 2: CMS plus IMI)

Figure 13. Elevations of Aspartate Aminotransferase (AST) and Total Bilirubin Among Subjects Receiving IMI/REL or IMI + Placebo in PN013

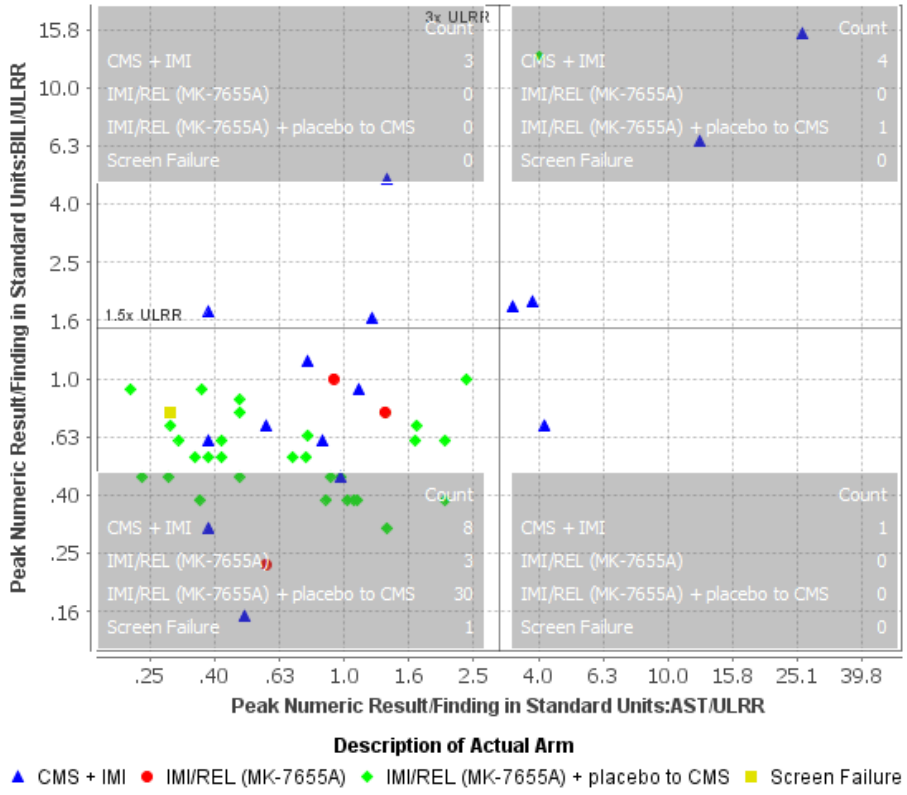
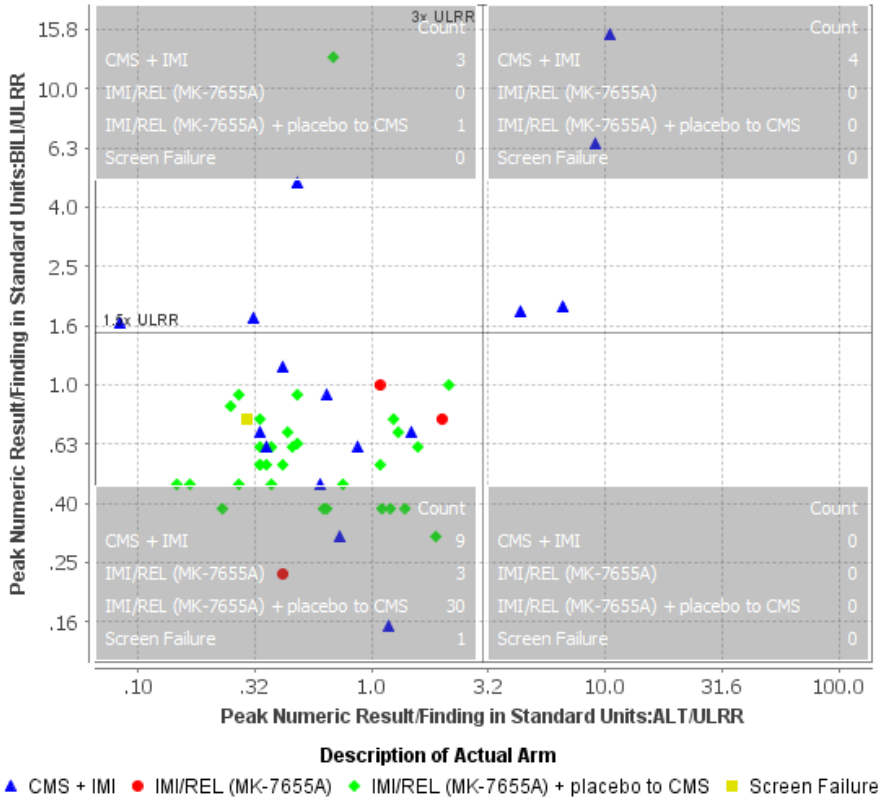


Figure 14. Elevations of Alanine Aminotransferase (ALT) and Total Bilirubin Among Subjects Receiving IMI/REL or IMI + Placebo in PN013



Overall, in PN003, PN004 and PN013, there were 25 subjects with liver transaminase elevations meeting the event of clinical interest (ECI) criteria defined as follows:

- Elevated AST or ALT ≥ to 5 X ULN
- Elevated AST or ALT laboratory value ≥ 3 X ULN and an elevated total bilirubin ≥ 2 X ULN and, at the same time, an alkaline phosphatase < 2 X ULN

Of these, the largest number, 14, were reported in PN004, the cIAI trial. Six cases were reported in PN013, of which five were in the comparator arm, CMS plus IMI. In PN003 and PN004, 16/431 (3.7%) subjects receiving IMI/REL 125mg or IMI/REL 250mg compared to 3/214 (1.4%) subjects receiving IMI plus Placebo reported liver transaminase elevations meeting the ECI criteria.

Reviewer Comment: The large number of liver transaminitis cases reported in PN004 is likely confounded by the abdominal injury in the majority of subjects enrolled in the trial. The small difference seen in transaminitis between subjects receiving IMI/REL compared to those receiving IMI alone or IMI plus CMS is also confounded by the fact that IMI is a component of all these regimens and has a known association with liver transaminitis. There were no cases of Hy's Law

or hepatic failure associated with the study drug (IMI/REL) reported in any of the trials. The majority of elevations in transaminases down trended and/or resolved by the end of follow up. There were no discontinuations of study medication due to transaminitis or other liver injury. Based on the results of these trials, we can conclude that there are elevations of liver transaminases seen with both IMI and IMI/REL and this is planned to be reflected in the label, in ***Section 6 Adverse Reactions****.*

7.4.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no clinical outcome assessments conducted as part of this drug development program.

7.4.7 Safety Analyses by Demographic Subgroups

Safety analyses were performed by the following demographic subgroups: sex, age, and renal function. The numbers for any racial/ethnic group apart from Caucasian were too small to conduct a meaningful analysis. Safety analyses by subgroups was conducted for PN003 and PN004 only. The sample size of PN013 was small (N=50) and did not allow for meaningful assessment of subgroup trends for safety.

Sex

Seven female subjects (3.2%) reported nausea compared to five male subjects (2.3%) in the IMI/ REL 250mg group, while the same number of subjects, 6 (2.8%) reported nausea among both males and females in the IMI plus Placebo group. Headaches were also reported more frequently in females in all treatment groups. Liver enzymes elevations including AST and ALT were about 2 to 4 times more frequently reported among males in the IMI/REL treatment groups compared to the IMI plus Placebo treatment group (Table 69). Differences among remainder of the AEs were too small to allow meaningful comparison between the different groups.

Reviewer Comment: The cause for the differences noted in liver enzyme elevations between male and female subjects is unclear. Some of the differences may be due to differences in severity of illness, underlying liver disease or concomitant medications. However due to the small numbers in each group, it is not possible to draw any definitive conclusions.

Table 69. Adverse Events Reported in ≥ 1% of Subjects Receiving IMI/REL or IMI/Placebo in PN003 and PN004 by Treatment Group and Sex

		IMI/REL 250 mg N=216 n (%)	IMI/REL 125 mg N=215 n (%)	IMI/Placebo N=214 n (%)

System Organ Class	MedDRA Preferred Term	Female	Male	Female	Male	Female	Male
Gastrointestinal disorders	Nausea	7 (3.2%)	5 (2.3%)	10 (4.6%)	5 (2.3%)	6 (2.8%)	6 2.8%)
	Diarrhea	4 (1.8%)	8 (3.7%)	7 (3.2%)	2 (0.9%)	4 (1.9%)	5 (2.3%)
	Vomiting	3 (1.4%)	4 (1.8%)	6 (2.7%)	4 (1.8%)	2 (0.9%)	2 (0.9%)
Nervous system disorders	Headache	7 (3.2%)	2 (0.9%)	3 (1.4%)	2 (0.9%)	3 (1.4%)	2 (0.9%)
Investigations	Alanine aminotransferase increased	2 (0.9%)	5 (2.3%)	1 (0.5%)	5 (2.3%)	3 (1.4%)	1 (0.5%)
	Aspartate aminotransferase increased	1 (0.5%)	5 (2.3%)	1 (0.5%)	6 (2.7%)	2 (0.9%)	1 (0.5%)
	Lipase increased	1 (0.5%)	2 (0.9%)	1 (0.5%)	1 (0.5%)	2 (0.9%)	2 (0.9%)
	Platelet count increased	2 (0.9%)	1 (0.5%)	0 (0.0%)	3 (1.4%)	0 (0.0%)	1 (0.5%)
	Blood alkaline phosphatase increased	1 (0.5%)	1 (0.5%)	3 (1.4%)	1 (0.5%)	2 (0.9%)	0 (0.0%)
Vascular disorders	Hypertension	0 (0.0%)	3 (1.4%)	3 (1.4%)	2 (0.9%)	0 (0.0%)	5 (2.3%)
	Phlebitis	0 (0.0%)	2 (0.9%)	2 (0.9%)	0 (0.0%)	2 (0.9%)	1 (0.5%)
General disorders and administration site conditions	Pyrexia	2 (0.9%)	3 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (0.9%)
Blood and lymphatic system disorders	Thrombocytosis	2 (0.9%)	3 (1.4%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	1 (0.5%)

Age

Adverse events were reported in similar rates between those 65 years and over and those under 65 years across all treatment groups in PN003 and PN004. A total of 38.1% (170/446) of subjects under 65 years of age experienced adverse events while 38.2% (76/199) of subjects 65 years of age or older experienced adverse events overall. GI disorders (nausea, diarrhea,

vomiting) and headache were more frequently reported in those under 65 years of age (Table 70). Other adverse events were reported in relatively small numbers overall limiting any significant comparison between age groups.

The three deaths reported in PN004, all occurred in subjects > 70 years of age. The incidence of SAEs was comparable among the 3 treatment groups in subjects ≥ 65 years of age.

Table 70. Adverse Events Reported in ≥ 1% of Subjects Receiving IMI/REL or IMI/Placebo in PN003 and PN004 by Treatment Group and Age Group

		IMI/REL 250 mg N=216 n (%)		IMI/REL 125 mg N=215 n (%)		IMI/Placebo N=214 n (%)	
System Organ Class	**MedDRA Preferred Term**	**< 65 years**	**>= 65 years**	**< 65 years**	**>= 65 years**	**< 65 years**	**>= 65 years**
Gastrointestinal disorders	Nausea	10 (4.6%)	2 (0.9%)	12 (5.5%)	3 (1.4%)	11 (5.1%)	1 (0.5%)
	Diarrhea	6 (2.7%)	6 (2.7%)	6 (2.7%)	3 (1.4%)	5 (2.3%)	4 (1.9%)
	Vomiting	7 (3.2%)	0 (0.0%)	9 (4.1%)	1 (0.5%)	4 (1.9%)	0 (0.0%)
Nervous system disorders	Headache	8 (3.7%)	1 (0.5%)	5 (2.3%)	0 (0.0%)	4 (1.9%)	1 (0.5%)
Investigations	Alanine aminotransferase increased	4 (1.8%)	3 (1.4%)	4 (1.8%)	2 (0.9%)	4 (1.9%)	0 (0.0%)
	Aspartate aminotransferase increased	3 (1.4%)	3 (1.4%)	5 (2.3%)	2 (0.9%)	3 (1.4%)	0 (0.0%)
	Lipase increased	2 (0.9%)	1 (0.5%)	2 (0.9%)	0 (0.0%)	4 (1.9%)	0 (0.0%)
	Blood alkaline phosphatase increased	2 (0.9%)	0 (0.0%)	4 (1.8%)	0 (0.0%)	1 (0.5%)	1 (0.5%)
	Platelet count increased	3 (1.4%)	0 (0.0%)	2 (0.9%)	1 (0.5%)	1 (0.5%)	0 (0.0%)
Vascular disorders	Hypertension	1 (0.5%)	2 (0.9%)	4 (1.8%)	1 (0.5%)	2 (0.9%)	3 (1.4%)
	Phlebitis	2 (0.9%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	2 (0.9%)	1 (0.5%)
General disorders and administration site conditions	Pyrexia	2 (0.9%)	3 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (0.9%)

Blood and lymphatic system disorders	Thrombocytosis	4 (1.8%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	2 (0.9%)	0 (0.0%)

APACHE II Score

A significant proportion of subjects in PN003 and PN004 had unknown APACHE scores. Those with higher APACHE II scores (>15) were few in number, 7 subjects in the IMI/REL treatment groups and 3 subjects in the IMI plus Placebo treatment group (Table 71). No significant conclusions can be drawn from differences in adverse event frequency by APACHE II score given the small sample size represented.

Reviewer Comment: Adverse events were more frequently reported in those with APACHE scores ≤ 15, however this is likely a reflection of the small numbers rather than a true assessment of the frequency of AEs in this population.

Table 71. Adverse Events Reported in ≥ 1% of Subjects Receiving IMI/REL or IMI/Placebo in PN003 and PN004 by Treatment Group and APACHE Score Group

		IMI/REL any dose[1] N=431[2] n (%)		**IMI/Placebo N=214 n (%)**	
		APACHE II Score Group			
System Organ Class	**MedDRA Preferred Term**	**<= 15 (N=105)**	**> 15 (N=7)**	**<= 15 (N=44)**	**> 15 (N=3)**
Gastrointestinal disorders	Nausea	16 (3.7%)	1 (0.2%)	8 (3.7%)	0 (0.0%)
	Diarrhea	13 (3.0%)	1 (0.2%)	4 (1.9%)	1 (0.5%)
	Vomiting	15 (3.4%)	1 (0.2%)	3 (1.4%)	0 (0.0%)
Nervous system disorders	Headache	4 (0.9%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Investigations	Alanine aminotransferase increased	8 (1.8%)	2 (0.5%)	4 (1.9%)	0 (0.0%)
	Aspartate aminotransferase increased	8 (1.8%)	2 (0.5%)	3 (1.4%)	0 (0.0%)
	Lipase increased	5 (1.1%)	0 (0.0%)	4 (1.9%)	0 (0.0%)
	Blood alkaline phosphatase increased	4 (0.9%)	0 (0.0%)	2 (0.9%)	0 (0.0%)

	Platelet count increased	6 (1.4%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Vascular disorders	Hypertension	3 (0.7%)	0 (0.0%)	4 (1.9%)	0 (0.0%)
	Phlebitis	4 (0.9%)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Blood and lymphatic system disorders	Thrombocytosis	2 (0.5%)	1 (0.2%)	2 (0.9%)	0 (0.0%)
General disorders and administration site conditions	Pyrexia	2 (0.5%)	1 (0.2%)	2 (0.9%)	0 (0.0%)

Source: Clinical Reviewer's Analysis
[1]*Includes IMI 500 mg/REL 250mg (IMI/REL 250mg) and IMI 500 mg/REL 125mg (IMI/REL 125mg)*
[2]*Includes subjects with unknown APACHE scores*

Renal function

There were no subjects with a baseline creatinine clearance <30 mL/min in PN003 and PN004. Decreased creatinine clearance does not appear to lead to increases in reported AEs across all treatment groups in the trials (Table 72).

Table 72. Adverse Events Reported in ≥ 1% of Subjects Receiving IMI/REL or IMI/Placebo in Studies PN003 and PN004 by Treatment Group and Creatinine Clearance

	IMI/REL any dose[1] N=431[2] n (%)			**IMI/Placebo N=214[2] n (%)**		
	Creatinine Clearance (mL/min)					
MedDRA Term	**< 60 to >= 30 (N=26)**	**< 90 to >= 60 (N=50)**	**>= 90 (N=88)**	**< 60 to >= 30 (N=20)**	**< 90 to >= 60 (N=17)**	**>= 90 (N=38)**
Nausea	1 (0.2%)	9 (2.1%)	17 (3.9%)	0 (0.0%)	0 (0.0%)	12 (5.6%)
Diarrhea	3 (0.7%)	6 (1.4%)	12 (2.7%)	3 (1.4%)	2 (0.9%)	4 (1.9%)
Vomiting	0 (0.0%)	4 (0.9%)	13 (3.0%)	0 (0.0%)	0 (0.0%)	3 (1.4%)
Headache	0 (0.0%)	3 (0.7%)	11 (2.5%)	1 (0.5%)	2 (0.9%)	2 (0.9%)
Alanine aminotransferase increased	4 (0.9%)	4 (0.9%)	5 (1.1%)	0 (0.0%)	2 (0.9%)	2 (0.9%)

Aspartate aminotransferase increased	4 (0.9%)	3 (0.7%)	6 (1.4%)	0 (0.0%)	1 (0.5%)	2 (0.9%)
Hypertension	2 (0.5%)	3 (0.7%)	3 (0.7%)	1 (0.5%)	1 (0.5%)	3 (1.4%)
Lipase increased	0 (0.0%)	2 (0.5%)	3 (0.7%)	1 (0.5%)	1 (0.5%)	2 (0.9%)
Blood alkaline phosphatase increased	0 (0.0%)	3 (0.7%)	3 (0.7%)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Thrombocytosis	2 (0.5%)	3 (0.7%)	1 (0.2%)	1 (0.5%)	0 (0.0%)	1 (0.5%)
Pyrexia	3 (0.7%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	1 (0.5%)	2 (0.9%)
Platelet count increased	0 (0.0%)	2 (0.5%)	4 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Phlebitis	1 (0.2%)	2 (0.5%)	1 (0.2%)	0 (0.0%)	1 (0.5%)	2 (0.9%)

Source: Clinical Reviewer's Analysis

Reviewer Comment: Safety analyses by demographic subgroups demonstrates that nausea was reported slightly more frequently among females in the IMI/REL treatment groups compared to the IMI plus Placebo treatment group. Headaches were also slightly more likely to be reported in females in all treatment groups. Liver enzymes elevations including AST and ALT were about 2 to 4 times more frequently reported among males in the IMI/REL treatment groups compared to the IMI plus Placebo treatment group.

GI disorders (nausea, diarrhea, vomiting) were more frequently reported in those under 65 years of age across all treatment groups. Headache was also more frequently reported in those under 65 years of age across all treatment groups. It is not clear why younger age groups are more likely to report these AEs.

Decreased creatinine clearance does not appear to lead to increases in reported AEs across all treatment groups in PN003 and PN004.

Overall, the small differences found in subgroup analyses do not inform meaningful clinical conclusions.

7.4.8 Specific Safety Studies/Clinical Trials

There were no additional specific safety studies or clinical trials conducted apart from those already described above.

7.4.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted in accordance with ICH S1A guidelines given that the continuous human use of IMI/REL is less than 6 months in duration.

Human Reproduction and Pregnancy

There are no adequate and well-controlled studies of IMI/REL or any of the components in pregnant women.

Pregnant and/or lactating women were excluded from enrollment into any of the clinical trials for IMI/REL. Additionally, no pregnancies were reported in any of the completed clinical trials.

In embryofetal developmental studies, imipenem/cilastatin (alone or in combination), showed no teratogenicity in mice, rats, rabbits, and monkeys at 1 to 5 times the recommended human dose based on body surface area.

In an embryofetal study in cynomolgus monkeys with IMI administered at doses similar to the recommended human dose based on body surface area, there was an increased association with embryonic loss during pregnancy.

In embryofetal developmental studies conducted with REL in mice, rats, and rabbits there was no evidence of reproductive or development toxicity with the exception of an increase in specific malformations in mice. In mice an increased litter incidence of skeletal malformations was observed with the high-dose of 450 mg/kg/day (approximately 6 times greater than the recommended human dose) and an increased litter incidence of cleft palate occurred in a non-dose dependent manner with a lower dose of 80 mg/kg/day (approximately equivalent to the recommended human dose based on AUC comparison). Fertility in male and female rats was not affected up to a dose of 450 mg/kg/day, which was the dose-limiting toxicity level and approximately 8-times the recommended human dose based on plasma AUC comparison. Also, in a pre-postnatal development study in rats, REL at doses up to 450 mg/kg/day did not impair the physical and behavioral development or reproduction of first-generation offspring.

Imipenem and cilastin are known to be excreted into breast milk in small quantities. REL has been shown to be excreted into the milk of rats, but it is not known whether it is excreted in human milk.

Pediatrics and Assessment of Effects on Growth

A deferral of pediatric assessment of IMI/REL for pediatric patients aged less than 18 years of age was requested by the Applicant on the grounds that IMI/REL will be ready for approval and use in adult patients before pediatric studies are completed in this age group and because additional safety and PK data in adults and older children are needed to support the initiation of studies. An initial Pediatric Study Plan (iPSP) for IMI/REL was agreed upon in January 2016. An amendment to the iPSP was provided with the submission of this NDA. Additional details on the iPSP and proposed amendments can be found in Section 9 Pediatrics.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdoses and drug abuse have not been reported in the IMI/REL clinical development

program. Doses higher than the proposed marketing dose of REL up to 1150mg were well-tolerated in Phase 1 trials, though these were single doses.

There is no inhibition of human or mammalian enzymes by REL identified through counter screening. Additionally, REL does not target a change in human physiology or biochemistry and targets bacterial enzymes (β-lactamases). For these reasons, withdrawal or rebound from REL is not expected.

Reviewer Comment: Overdose and drug abuse, as well as with withdrawal and rebound potential is unlikely with IMI/REL given the biological properties of REL and the settings in which it will be used, as well as experience with other β-lactamase inhibitors and IMI alone. IMI/REL can be removed by hemodialysis, although no specific clinical information is available on use of hemodialysis to treat overdose.

7.4.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

IMI/REL has not been marketed in the United States or outside the United States. There is no postmarketing experience for this drug.

Imipenem/cilastatin, a component of IMI/REL has been approved for use in the United States since 1985. Adverse reactions identified during postmarketing use of imipenem/cilastatin include the following:

- Gastrointestinal:
  - Hepatitis (including fulminant hepatitis), hepatic failure, staining of the teeth and/or tongue
- Hematologic:
  - Pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, hemolytic anemia
- CNS
  - Tremor, psychiatric disturbances including hallucinations, dyskinesia, agitation
- Special Senses
  - Taste perversion
- Skin
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
- Body as a whole
  - Drug fever
- Renal
  - Acute renal failure
  - Urine discoloration

Expectations on Safety in the Postmarket Setting

Given the history with imipenem/cilastatin in the postmarket setting and the absence of new safety signals in the IMI/REL development program thus far, no specific safety concerns are presently anticipated. However, it should be noted that the clinical experience with relebactam has been limited.

7.4.11 Integrated Assessment of Safety

Safety data were integrated for the 7 Phase 1 trials. These data were not integrated with PN003, PN004 or PN013 trials due to differences in dosing regimens and study populations.

Safety data were also integrated for PN003 and PN004 due to similarities in dosing regimen and study design. However, PN013 was not integrated with these two trials due to differences in study populations and study design.

Deaths

There were 11 deaths in the PN003, PN004 and PN013. There were no deaths reported in the Phase 1 trials. Three deaths occurred during the follow-up period of PN003 and PN004, (all in the cIAI trial, and 2 deaths occurred outside the follow-up period, all in the cUTI trial (Table 54 and Table 55). There were 6 deaths in PN013, five in the randomized and one in the open label arms (Table 56). None of the reported deaths were deemed to be related to relebactam and no association between death and the dose of relebactam was suggestive.

SAEs

Serious adverse events occurred in a total of 4.7% (30/645) subjects: 3.2% (7/216) of subjects receiving IMI/REL 250mg, 5.6% (12/215) patients receiving IMI/REL 125mg and 5.1% (11/214) of patients receiving IMI/Placebo. Given that there was no association between the dose of relebactam and the incidence of SAEs and the rates of SAEs in subjects treated with IMI/REL 250 mg were lower than in subjects receiving placebo, the observed differences in the rates of SAEs between the trial arms are probably related to chance findings and do not suggest an association between relebactam and SAEs.

The most commonly reported SAEs in the pooled IMI/REL treatment arms included diarrhea, acute kidney injury, ventricular fibrillation and *Clostridium difficile* infection (Table 58). There was one case of ventricular fibrillation in the IMI/REL arms resulting in death; the relationship of ventricular fibrillation to the study drug is uncertain however.

Discontinuations

Discontinuations occurred at a similar rate between the IMI/REL treatment arms (2.3%: 10/431) and the IMI/Placebo treatment arm (2.3%: 5/214) in the ISS safety population. The most

frequent cause of discontinuation of study drug was diarrhea in the ISS population. There were no discontinuations of IV study drug in Treatment Group 1 (IMI/REL) in Study PN013. One discontinuation in the open-label, non-randomized Treatment Group 3 (IMI/REL) was due to generalized tonic-clonic seizure.

Adverse Events

The most common AEs reported in the ISS safety population were gastrointestinal disorders including nausea, diarrhea and vomiting (Table 62). GI-related AEs were more frequently reported in subjects receiving IMI/REL. Liver transaminase elevations for ALT, AST and alkaline phosphatase were also more frequently reported in subjects receiving IMI/REL compared to those receiving IMI + Placebo, however the differences were small and not clinically meaningful.

Renal injury occurred in similar rates between the two treatment groups. Infusion site reactions occurred slightly more frequently in the IMI/REL treatment group with 6 subjects (1.4%) in IMI/REL treatment group and 0 subjects in IMI + Placebo treatment group. Neurological and psychiatric CNS disorders were also slightly more frequently reported in the IMI + Placebo group compared to the IMI/REL treatment group. These differences were small and not clinically meaningful.

The overall similarity in AE rates between IMI/REL and IMI alone suggests the safety profile of IMI/REL and IMI is comparable.

In PN013, adverse events were overall more frequently reported than in PN003 or PN004, likely due to the increased morbidity of the population and the less stringent enrollment criteria. Adverse reactions occurred in 71% (22/31) of patients receiving IMI/REL compared to 81.3% (13/16) of patients receiving colistin plus IMI. Significant AEs included increased LFTs, infusion site reactions, anemia, and creatinine/renal injury. With the exception of anemia, which was more frequently reported in the IMI/REL treatment arm (9.7% vs. 12.5%), increased LFTs, infusion site reactions and creatinine/renal injury were all more frequently reported in the comparator, IMI + CMS treatment arm.

7.5 Statistical Issues

Trials PN003 and PN004 were not designed or powered for the NI assessments using the appropriate analysis population and endpoints. All three trials were considered descriptive and not adequate and well-controlled trials. There were no major statistical issues concerning safety data or analysis.

7.6 Conclusions and Recommendations

Efficacy

Efficacy assessment of RECARBRIO relies in part on the FDA's previous findings of efficacy for imipenem in the treatment of cUTI and cIAI, *in vitro* and animal data demonstrating that relebactam restores activity of imipenem against imipenem-nonsusceptible gram-negative organisms expressing some Class A and some Class C β-lactamases, and by the probability of target attainment (PTA) analyses for relabactam conducted by the FDA. Studies PN003 in cUTI and PN004 in cIAI compared IMI/REL 250 mg to IMI alone and were primarily designed for safety and dose-selection assessment. Study PN013 was not designed for hypothesis testing.

Please see section 7.3.4 Assessment of Efficacy Across Trials for further detailed assessment of efficacy in these trials.

Safety

The safety of IMI/REL was supported by a total of 10 trials, 7 Phase 1 trials, 2 double-blind, randomized trials, one each in cUTI and cIAI, and 1 double-blind, randomized trial in imipenem-resistant cUTI, cIAI, and HABP, which evaluated a fixed dose combination of IMI/REL compared to IMI + Colistin. The safety database was considered sufficient for the purposes of this NDA, particularly given the clinical experience with imipenem-cilastatin. The safety review focused on studies PN003, PN004 and PN013.

Overall, no major safety signals emerged during the analyses of trials PN003 and PN004. The safety profiles of IMI/REL and IMI were found comparable and no meaningful differences in safety of the two doses of relebactam studied in these trials, i.e., 125 mg and 250 mg, were evident.

In general, the AEs observed were consistent with prior knowledge of the safety of imipenem/cilastatin, a component of IMI/REL. While slight differences between trial arms were seen in frequency of certain AEs such as GI disorders and liver enzyme elevations, the differences were small, and there was no clear causality linking relebactam to the specific AEs that were noted to be increased in the IMI/REL treatment groups.

In study PN013, the treated population was small which limited our ability to draw meaningful safety conclusions. However, in general the rates of AEs, SAEs, and discontinuations were lower in the IMI/REL treatment arm compared to the comparator arm, IMI + CMS.

8 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for this NDA as there were no specific issues that required expert input.

9 Pediatrics

There were no pediatric studies submitted with this NDA. An initial Pediatric Study Plan (iPSP) was submitted to IND 108754 for IMI/REL and was agreed to by the Agency on 21 January 2016. The iPSP requested a deferral of pediatric assessments for patients aged less than 18 years of age as studies in this age group were not yet completed and additional safety and PK data in adults and older children were needed to support the initiation of the studies.

An amendment to the iPSP was submitted with this NDA and was reviewed by the PeRC on 11 June 2019. Because there were no major changes to the proposed number and type of studies or to the timeline and involve details of the protocols a new agreed iPSP was not needed.

The pediatric development plan includes the following studies:

PN020: An open-label, single dose study to evaluate the PK, safety, and tolerability of imipenem/cilastatin/relebactam in children from birth to less than 18 years of age with proven or suspected gram-negative infections. The trial is currently ongoing.

PN021: A randomized, open-label active controlled trial to evaluate the safety and tolerability of imipenem/cilastatin/relebactam in children from birth to less than 18 years of age with cUTI or cIAI.

(b) (4)

10 Labeling Recommendations

Labeling recommendations provided by the multidisciplinary review team, including OPDP and DMEPA have been incorporated in labeling. The trade name RECARBRIO was considered acceptable by DMEPA. Only the results of the cUTI and cIAI trials are described in the Adverse Reactions section of the label. The comparative rates of adverse reactions for imipenem/cilastatin/relebactam and imipenem/cilastatin groups are provided for the imipenem/cilastatin/relebactam 250 mg group as this is the dose recommended for marketing.

The Clinical Studies section (section 14 of labeling) indicates that the determination of efficacy of imipenem/cilastatin/relebactam was supported in part by the previous findings of the efficacy and safety of imipenem/cilastatin for the treatment of cIAI and cUTI whereas the contribution of relebactam was primarily established in vitro and in animal models of infection. The section states that imipenem/cilastatin/relebactam was studied in two randomized, blinded, active-controlled, multicenter trials, one each in cIAI and in cUTI including pyelonephritis without describing the trials. (b) (4)

Labeling also includes warnings, adverse reactions, and drug-drug interaction information from the imipenem label.

Of note, the final version of the label was still under revision at the time of review completion.

11 Risk Evaluation and Mitigation Strategies (REMS)

There are no risk evaluation or mitigation strategies proposed for this NDA.

12 Postmarketing Requirements

The following postmarketing requirements (PMR) are required for this application under the Pediatric Research and Equity Act (PREA):

1) Conduct an open-label, single-dose study to evaluate the pharmacokinetics, safety and tolerability of imipenem/cilastatin/relebactam in children from birth to less than 18 years of age with proven or suspected gram-negative infections

2) Conduct a randomized, open-label, active controlled trial to study the safety, tolerability, and efficacy of imipenem/cilastatin/relebactam in children from birth to less than 18 years of age subjects with complicated urinary tract infection or complicated intra-abdominal infection.

The following PMR is required under 505(o) the Federal Food, Drug, and Cosmetic Act (FDCA):

1) Conduct a United States surveillance study for five years from the date of marketing to determine if resistance to imipenem/cilastatin/relebactam has developed in the organisms specific to the indications in the label.

APPEARS THIS WAY ON ORIGINAL

13 Division Director (Clinical) Comments

I concur with the review team's assessment and recommendations.

14 Office Director Comments

I concur with the review team's assessment and recommendations.

15 Appendices

15.1 References

1. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269–284. doi: 10.1038/nrmicro3432.
2. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S, National Healthcare Safety Network T et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. Infection control and hospital epidemiology: the official journal of the Society of Hospital Epidemiologists of America. 2013;34(1):1–14.
3. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adult and children: guidelines by the surgical infection society and the infectious diseases society of America. Clin Infect Dis. 2010;50:133–164.
4. Hawser S, Hoban DH, Badal RE, et al. Epidemiology and antimicrobial susceptibility of Gram-negative aerobic bacteria causing intra-abdominal infections during 2010-2011. J Chemother. 2015;27:67–73.
5. Sartelli M, Catena F, Ansaloni L, et al. Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study. World J Emerg Surg. 2012;7:36.
6. World Health Organization: Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017. Accessed Jan 23 2019. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1.
7. CDC's Antibiotic Resistance Patient Safety Atlas 2016. Atlanta: Centers for Disease Control and Prevention; 2016 (http://www.cdc.gov/hai/surveillance/ar-patientsafety-atlas.html, accessed 26 October 2017).
8. Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities. Geneva: World Health Organization; 2017.
9. Ben-David D, Kordevani R, Keller N, Tal I, Marzel A, Gal-Mor O, et al. Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections. Clin Microbiol Infect 2012;18:54-60.
10. Queenan AM. Carbapenemases: the versatile beta-lactamases. Clin Microbiol Rev 2007; 20: 440-58.
11. Canton R, Carmeli Y, Giske CG, Glupcyzynski Y, Gniadkowski M, Livermore DM, et al. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect 2012;18:413-31.
12. Simner PJ, Johnson JK, Brasso WB, Anderson K, Lonsway DR, Pierce VM, et al. Multicenter evaluation of the modified carbapenem inactivation method and the Carba NP for detection of carbapenemase-producing Pseudomonas aeruginosa and Acinetobacter baumannii. J Clin Microbiol 2018;56: pii: e01369-17.
13. Lob SH, Karlowsky JA, Young K, Motyl MR, Hawser S, et al. Activity of imipenem/relebactam against MDR Pseudomonas aeruginosa in Europe: SMART 2015-17. J Antimicrob Chemother, 2019:dkz191, https://doi.org/10.1093/jac/dkz191.
14. Castanheira M, Davis AP, Mendes RE, Serio AW, Krause KM, Flamm RK. In vitro activity of plazomicin against gram-negative and gram-positive isolates collected frm United States hosptials and omparative activity of aminoglycosides against carbapenem-resistant Enterobaccteriaceae and isolates carrying carabpenemase genes. Antimicrob. Agents Chemother. 2018; 62: e00313-18.
15. A. Martins, Tuon F, Bail L et al. Antimicrobial activity of plazomicin against Enterobacteriaceae producing carbapenemases from 50 Brazilian medical centers. Diagno Microbiol Infect Dis. 2018;90: 228-232.

15.2 Financial Disclosure

Financial disclosure information was provided for the investigators who conducted studies PN003, PN004 and PN013 evaluating IMI/REL for the limited indications under cUTI and cIAI.

The Applicant determined there were no financial interests or arrangements to disclose for the investigators in these studies.

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 384		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):0 Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ **N/A**	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ **N/A**	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐ **N/A**	No ☐ (Request explanation from Applicant)

15.3 Nonclinical Pharmacology/Toxicology

15.4 OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1 In Vitro studies

Plasma Protein Binding

The binding of REL to human plasma proteins was determined by ultracentrifugation. The ^{3}H-labeled REL ([^{3}H]REL) was mixed with mouse, rat, monkey and human plasma to concentrations of 5 and 50 µM. Binding was independent of REL concentrations with mean unbound fractions of 79%, 82.8%, 90.4% and 77.9% in mouse, rat, monkey and humans, respectively (Study PK002MK7655).

Blood-to-Plasma Partitioning

To determine the blood-to-plasma concentration ratio, [^{3}H]REL was mixed with fresh whole blood to a final concentration of 5 and 50 µM. The blood-to-plasma ratio was calculated by dividing the radioactivity in the blood fraction by the radioactivity in the plasma fraction. The blood-to-plasma concentration ratio of [^{3}H]REL ranged from 0.59 to 0.63 following in vitro incubations with mouse, rat, monkey, and human blood and was independent of REL concentration (Study PK002MK7655).

Metabolism of [^{3}H]REL

REL undergoes minimal metabolism in humans. The in vitro metabolic turnover of [^{3}H]REL was evaluated in phosphate buffered saline and in mouse, rat, monkey, and human plasma at 37 °C over 4 hr. The degradation/metabolism of [^{3}H]REL was <10% in PBS buffer, and in human, mouse, rat, and monkey plasma. The metabolic turnover also was minimal (<3%) in human, rat, and monkey hepatocytes following incubation at 37ºC for 2 hr. Thus, enzymes involved in the metabolism of REL were not further investigated. The metabolite M1 was reported as a degradation product, suggesting that the formation of M1 could be non-enzymatic (Study PK002MK7655).

The negligible in vitro metabolic turnover of REL is consistent with the minimal metabolism observed in vivo. In Study PN001, REL was 98.4% and 99.6% excreted in the urine as the parent drug in the two dosing groups that received a single dose of 250 mg. Similarly, in the multiple dose arm, the mean percentage of REL dose excreted unchanged in urine was 90.8% at 250 mg, 99.5% at 125 mg and 95.2% at 375 mg. These results indicate that REL is cleared primarily (>90%) via urinary excretion of the parent drug in humans. Plasma samples from Study PN001 were profiled for circulating metabolites by high resolution mass spectrometry and REL was the only drug-related component detected in human plasma. Based on these data, we agreed that a human ADME study with radiolabeled REL does not need to be conducted.

Inhibition of CYP Isozymes by REL (Study PK002MK7655)

The reversible inhibitory potential of REL towards major human liver CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was evaluated in vitro using human liver microsomes. At concentrations up to 100 µM, REL was not an inhibitor (IC50 >100 µM) of any of the CYP isoforms.

Time-dependent inhibition of CYP3A4 was evaluated in pooled human liver microsomes (1 mg/mL) that were preincubated for 5 to 30 min in the presence of an NADPH generating system at 37°C with 10 and 50 µM REL. REL did not cause time-dependent inhibition of CYP3A4 activity at either concentration.

Induction of CYP3A4, CYP2B6 and CYP1A2 (Studies PK002MK7655 and PK007MK7655)

The potential for REL to induce CYP1A2, CYP2B6, and CYP3A4 was evaluated in plated human hepatocytes from three donors. REL was incubated with hepatocytes for 48 hours, and both messenger ribonucleic acid (mRNA) and enzyme activity were measured. REL showed no in vitro induction of CYP1A2, CYP2B6, or CYP3A4, with little or no increase in mRNA and enzyme activity levels.

The potential for REL to induce CYP1A2, CYP2B6, and CYP3A4 was evaluated in plated human hepatocytes from three donors. REL was incubated with hepatocytes for 48 hr, and both messenger ribonucleic acid (mRNA) and enzyme activity were measured. REL showed no in vitro induction of CYP1A2, CYP2B6, or CYP3A4, with <15% increase in mRNA and enzyme activity from the corresponding positive controls.

Evaluation of REL as a Substrate of Renal Transporters: OAT1, OAT3, OAT4 and OCT2 (Studies PK004MK7655, PK006MK7655 and PK012MK7655)

The uptake of 2 µM REL was evaluated in MDCKII cells stably transfected with human renal uptake transporter OAT1 and OAT3, in HEK293 cells transiently transfected with OAT4, and in CHO-K1 cells stably transfected with OCT2. The data indicate that REL is a substrate of OAT3 and OAT4, but not a substrate of OAT1 and OCT2. The OAT3-mediated uptake of REL was concentration-dependent, without reaching saturation at the highest concentration tested (100 µM). These data suggest that OAT3-mediated transport of REL is a high capacity process and is likely not saturated at the clinically relevant drug concentrations (Cmax ~50 µM).

In the clinical DDI study of IMI/REL with probenecid (Study PN019), an inhibitor of OATs, AUC of relebactam and imipenem increased 24% and 16% when co-administered with probenecid, respectively (See Section 15.4.3).

Evaluation of REL as a Substrate of Efflux Transporters

The bi-directional transport of [^{14}C]REL (1 µM) was evaluated in LLC-PK1 cells stably expressing human and rat P-gp, and in MDCKII cells stably expressing human BCRP. Under the conditions tested, the apparent permeability (Papp) of REL was too low to reliably assess P-gp and BCRP transport. Since the low permeability of REL precluded a reliable substrate assessment for P-gp and BCRP in the bi-directional assay, membrane vesicle studies were conducted to further

evaluate whether REL is a substrate of P-gp and BCRP, as well as other efflux transporters including MRP2, and MRP4.

P-gp, BCRP, MRP2, and MRP4 (Studies PK009MK7655 and PK012MK7655)
The in vitro studies using membrane vesicles isolated from baculovirus infected Spodoptera frugiperda (Sf9) cells containing human P-gp, BCRP, MRP2, and MRP4 indicate that REL is not a substrate of these efflux transporters as REL showed similar uptake in transporter-containing vesicles compared to the control vesicles.

MATE1 and MATE2 (Studies PK009MK7655 and PK012MK7655)
Uptake of [^{14}C]REL was evaluated in vitro in CHO-K1 cells stably transfected with MATE1 and in MDCKII cells stably transfected with MATE2K. The fold difference in [^{14}C]REL uptake between the transfected cells and the parent cells were 2.6 and 2.0 for MATE1 and MATE2K, respectively, indicating that REL is a substrate of MATE1 and MATE2K. The corresponding fold difference in metformin, a positive control, uptake was 20 and 6.4 for MATE1 and MATE2K, respectively.

Evaluation of REL as an Inhibitor of Drug Transporters (Studies PK008MK7655 and PK009MK7655)
The potential for REL to inhibit major human drug transporters, including P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2K, BCRP, or BSEP, was evaluated in vitro. REL was not found to be an inhibitor of the transporters evaluated (IC50 >300 μM).

15.4.2 Preclinical PK/PD Studies

This application relied on a limited clinical program. Efficacy conclusions drawn from PN003 and PN004 were limited as these trials compared IMI/REL to IMI alone. The contribution of REL could not be evaluated because these studies included a limited number of IMI resistant isolates. PN013 was limited in size and was designed as a descriptive trial with no statistical comparative efficacy assessments.

Thus, additional evidence of effectiveness was derived from pre-clinical PK/PD studies. Dose fractionation and dose response studies in murine thigh and lung models were performed to evaluate the in vivo activity of IMI/REL (Studies PD006 and PD040). In vitro hollow fiber infection model (HFIM) experiments were performed to evaluate the antibacterial activity and suppression of resistance of IMI and IMI/REL (Study PD031). The Applicant used these HFIM data to derive an estimated IMI % *f*T>MIC target of 6.5% for 2-log kill. However, the Agency used these data to assess the added contribution of REL to the antibacterial effect of IMI. The Agency has determined that the Applicant has demonstrated a contribution of REL based on these nonclinical and *in vitro* data despite the lack of clinical effectiveness data.

Hollow Fiber PK/PD Time-Kill Studies (Study PD031)

To demonstrate the projected efficacy of the selected PN003 and PN004 doses against imipenem resistant *P. aeruginosa* and *K. pneumoniae* strains, a number of time-kill studies utilizing an in vitro PK/PD hollow fiber cell culture system were conducted. Imipenem MIC values were determined in the presence of 4 µg/mL REL, hereafter referred as the "potentiated MIC" (pMIC).

Study PD031 was conducted with 15 imipenem-resistant Enterobacteriaceae (n=11) and *P. aeruginosa* strains (n=4). Bacteria were exposed to the pharmacokinetic profiles of IMI and REL that simulated the free drug exposures in humans at a dose of 500 mg IMI q6h in combination with either 125 mg or 250 mg REL q6h, with each dose given as a 30-minute IV infusion. Samples for PD analysis were collected up to 70 hours post dose for colony counting. IMI alone (500 mg q6h) and no drug growth control arms were also conducted with each isolate. An initial bacterial density of approximately 1 to 3 × 10^5 CFU/mL was inoculated into the extracapillary space of the pre-conditioned hollow fiber cartridges. Inoculated hollow fiber cartridges were incubated at 37°C for 4 hours and reached approximately 1 × 10^6 CFU/mL at the time of the first dose. IMI MICs and pMICs of bacterial isolates are highlighted Table 73.

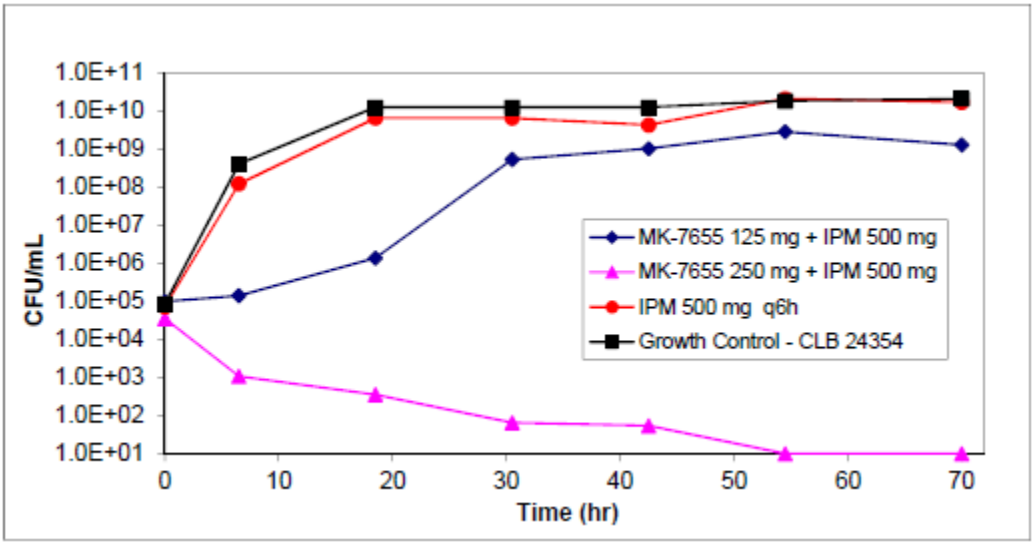
Table 73. PD Results from Hollow Fiber Model (Study PD031)

				Hollow fiber results	
Organism	Isolate Number	IMI MIC	pMIC	IMI + 125 mg REL	IMI + 250 mg REL
Pseudomonas aeruginosa	CLB 24227	16	2	>4 log kill with no regrowth up to 70 hr	>4 log kill with no regrowth up to 70 hr for all experiments
Pseudomonas aeruginosa	CLB 24228	32	8		
Pseudomonas aeruginosa	CLB 24226	32	4		
Klebsiella pneumoniae	CL 6339	64	1		
Pseudomonas aeruginosa	CLB 24354	64	16	Regrowth starting at 6 hr	
Klebsiella pneumoniae	CL 6569	256	4	ND	
Klebsiella pneumoniae	CLB 26410	>256	8	ND	
Klebsiella pneumoniae	CL 5763	32	0.5	ND	
Klebsiella pneumoniae	CL 6838	16	0.5	ND	
Escherichia coli	IHMA 1224137	8	≤0.5	ND	
Escherichia coli	IHMA 1231530	4	≤0.5	ND	
Klebsiella pneumoniae	IHMA 516426	16	0.5	ND	
Serratia marcescens	IHMA 1203541	8	1	ND	
Klebsiella oxytoca	IHMA 1211369	32	0.25	ND	
Klebsiella pneumoniae	IHMA 520284	16	0.25	ND	

ND = Not determined; REL = relebactam; IMI = imipenem

Both 125 mg and 250 mg doses of REL coadiminstered with IMI 500 mg showed rapid and sustained bactericidal activity against the *P. aeruginosa* strains CLB 24227, CLB 24228, and CLB 24226 (IMI MIC values of 16 to 32 µg/mL). In contrast, when the two IMI/REL combinations were tested against the *P. aeruginosa* strain CLB 24354 that had high resistance to imipenem (MIC 64 µg/mL), the lower dose of REL (125 mg) was not efficacious, and it took a longer time (>50 hours) for REL 250 mg to reduce the CFU to below detectable limits (**Figure 15**).

Figure 15. Hollow Fiber Efficacy Study of "125 mg" and "250 mg" Doses for Relebactam in Combination with Imipenem against *P. aeruginosa* CLB 24354



There were three Enterobacteriaceae isolates that did not show a benefit to the addition of REL *vs.* IMI alone (Figure 16, Figure 17 and Figure 18). It should be noted that the expression of the beta-lactamases was not confirmed during these experiments.

Figure 16. Hollow Fiber Efficacy Study of "250 mg" Dose for Relebactam in Combination with Imipenem against *E. coli* IHMA 1231530

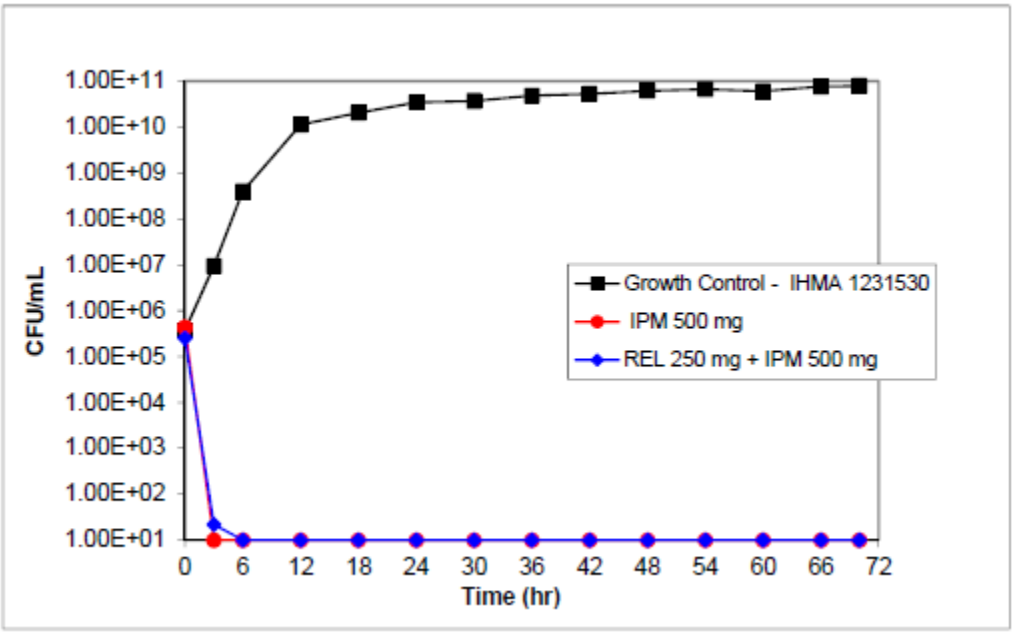


Figure 17. Hollow Fiber Efficacy Study of "250 mg" Dose for Relebactam in Combination with Imipenem against *K. pneumoniae* IHMA 516426

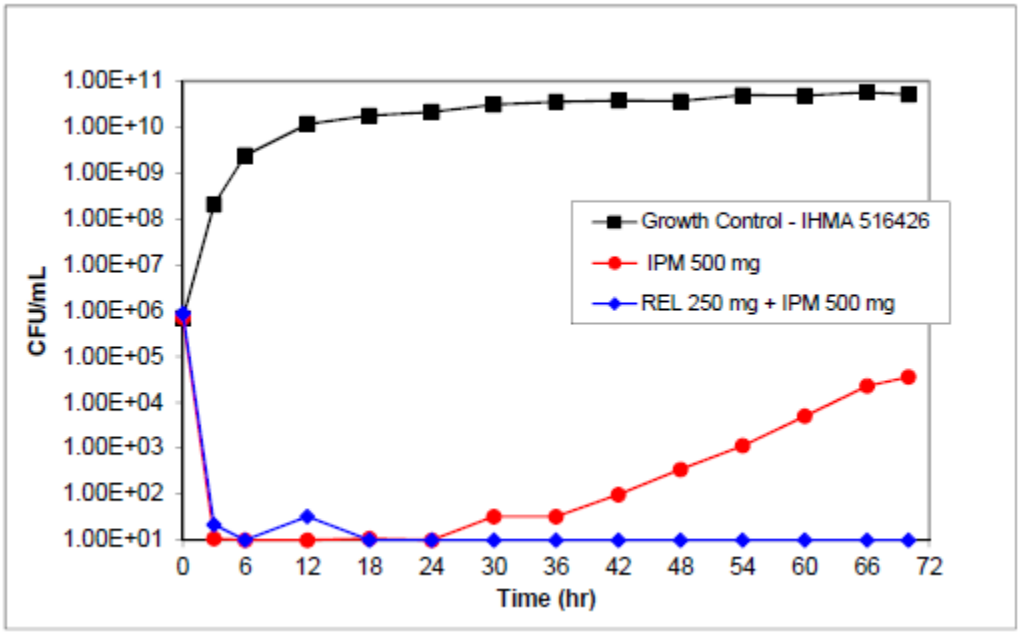
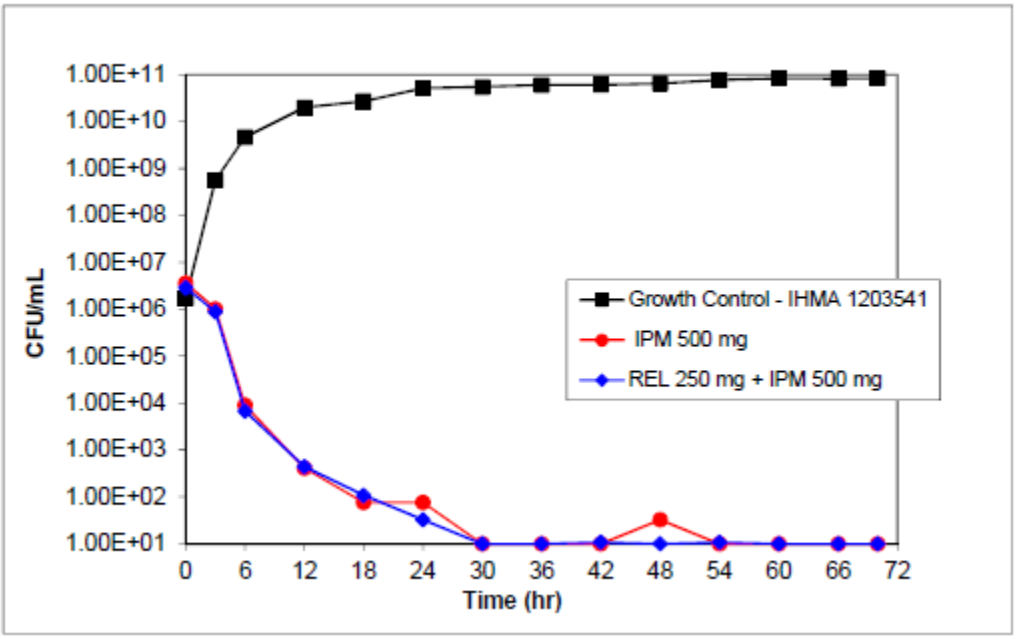


Figure 18.Hollow Fiber Efficacy Study of "250 mg" Dose for Relebactam in Combination with Imipenem against *S. marcescens* IHMA 1203541



Assessment of In Vivo Efficacy of REL in Combination with IMI in Murine Infection Models of Infection (Studies PD006 and PD040)

Several neutropenic mouse models of infection were used to determine the in vivo efficacy of REL co-administered with IMI/CIL. The PK data from the murine lung studies were used to build a mouse population PK model (Study PD006 and PD040).

In Study PD006, two imipenem-resistant clinical strains, *P. aeruginosa* strain CLB 24228 (imipenem MIC of 32 µg/mL which is reduced to 8 µg/mL in the presence of 4 µg/mL REL) and *K. pneumoniae* strain CL 6339 (imipenem MIC of 64 µg/mL, which is reduced to 4 µg/mL in the presence of 2 µg/mL of REL). Combination treatment was delivered by 1-hour IV infusion every 6 hours. A static response to therapy was used as the endpoint for clinical efficacy. Blood was sampled via the tail vein at 20, 40, 75, and 105 minutes after the start of the fourth infusion (designated 1/3T, 2/3T, T+15, T+45, respectively) to determine REL concentrations.

IMI/REL showed efficacy in murine models of infection, both disseminated infections such as septicemia and organ-specific infections.

Table 74. Efficacy of REL in a Disseminated Model of Infection with Imipenem-resistant *P. aeruginosa* (PATOA 01-08)

Dose (mg/kg IV as a 60 min infusion q6h for 24 hours)		Total Log_{10} CFU	Change Log_{10} CFU Compared to Sham-treated	Relebactam Plasma Concentration
Imipenem	Relebactam			

			Control	(µM at 2/3T)
N/A	N/A	6.78	N/A	N/A
5	N/A	6.33	-0.45	N/A
5	40	3.05	-3.73	202
5	20	3.65	-3.13	108
5	10	5.06	-1.72	58

2/3T = 40 minutes after the start of infusion; N/A = not applicable

Table 75. Efficacy of REL in a Pulmonary Model of Infection with Imipenem resistant *P. aeruginosa* (PATOLA 01-08)

Dose (mg/kg IV as a 60 min infusion q6h for 24 hours)		Total Log10 CFU	Change Log10 CFU Compared to Sham-treated Control	Relebactam Plasma Concentration (µM at 2/3T)
Imipenem	Relebactam			
N/A	N/A	6.59	N/A	N/A
5	N/A	6.70	+0.11	N/A
5	80	2.00	-4.59	175
5	40	3.00	-3.59	140
5	20	4.22	-2.37	42

2/3T = 40 minutes after the start of infusion; N/A = not applicable

Table 76. Efficacy of REL in a Pulmonary Model of Infection with Imipenem resistant *P. aeruginosa*: Comparison of 24 Hour vs. 48 Hour Dosing (PATOLA 02-08; 24/48 hr dosing)

Dose (mg/kg IV as a 60 min infusion q6h for 24 hours)		Total Log10 CFU		Change Log10 CFU Compared to Imipenem/Cilastatin Group	
Imipenem	Relebactam	24 hr	48 hr	24 hr	48 hr
N/A	N/A	6.22	[1]ND	N/A	N/A
5	N/A	6.10	7.57	N/A	N/A
5	40	2.91	3.00	-3.19	-4.57
5	20	4.08	4.59	-2.02	-2.98

1 Animals did not survive to 48 hr
CFU = colony-forming unit(s); hr = hours; IV = intravenous; mg/kg = milligram per kilogram; N/A = not applicable; ND = not determined; q6h = every 6 hours

Table 77. Efficacy of REL in a Disseminated Model of Infection with Imipenem-resistant K. pneumoniae (KLEBTOA 02-08)

Dose (mg/kg IV as a 60 min infusion q6h for 24 hours)		Total Log10 CFU	Change Log10 CFU Compared to Sham-treated Control	Relebactam Plasma Concentration (uM at 2/3T)
Imipenem	Relebactam			
N/A	N/A	6.15	N/A	N/A

5	N/A	6.67	+0.52	N/A
5	80	3.46	-2.69	105
5	40	3.09	-3.06	87
5	20	3.86	-2.29	40

2/3T = 40 minutes after the start of infusion; CFU = colony-forming unit(s); IV = intravenous; µM = micromolar;mg/kg = milligram per kilogram; N/A = not applicable; q6h = every 6 hours

Table 78. Efficacy and Plasma Exposure of REL in Combination with Imipenem/Cilastatin in a Delayed Therapy *P. aeruginosa* Lung Infection Model (PATOLA 04-08)

[1]Time Post-infection (hr)	Dose (mg/kg IV as a 60 min infusion q6h for 24 hours)		Total Log10 CFU (SD)	Change Log10 CFU from 16.5 hr	Relebactam Plasma Concentration (uM at 2/3T)
	Imipenem	Relebactam			
16.5	N/A	N/A	5.04 (0.556)	N/A	N/A
24	N/A	N/A	5.99 (0.478)	+0.95	N/A
40	N/A	N/A	7.92 (0.472)	+2.88	N/A
40	5	N/A	7.14 (0.800)	+2.10	N/A
40	5	80	5.80 (0.775)	[3]+0.76	217.5
40	5	40	[2]5.86 (0.186)	[3]+0.82	121.1
40	5	20	4.98 (0.802)	[3]-0.06	37.8

1 Five animals per group
2 Three animals per group
3 Not significantly different from CFU burden at start of therapy at 16.5 hours
2/3T = 40 minutes after the start of infusion; CFU = colony-forming unit(s); IV = intravenous; µM = micromolar;mg/kg = milligram per kilogram; N/A = not applicable; q6h = every 6 hours

Table 79. Efficacy and Plasma Exposure of REL in Combination with Imipenem/Cilastatin in a Delayed Therapy *P. aeruginosa* Lung Infection Model (PATOLA 05-08)

[1]Time Post-infection (hr)	Dose (mg/kg IV as a 60 min infusion q6h for 24 hours)		Total Log10 CFU (SD)	Change Log10 CFU from 16.5 hr	Relebactam Plasma Concentration (uM at 2/3T)
	Imipenem	Relebactam			
16.5	N/A	N/A	4.91 (0.736)	N/A	N/A
24	N/A	N/A	5.84 (0.930)	+0.93	N/A
40	N/A	N/A	6.96 (0.358)	+2.05	N/A
40	5	N/A	7.11 (0.501)	+2.20	N/A
40	5	40	5.09 (0.355)	[2]+0.18	65.0
40	5	20	4.99 (0.596)	[2]+0.08	44.3
40	5	10	6.46 (0.772)	+1.55	23.3

1 Five animals per group
2 Not significantly different from CFU burden at start of therapy at 16.5 hours

2/3T = 40 minutes after the start of infusion; CFU = colony-forming unit(s); IV = intravenous; µM = micromolar; mg/kg = milligram per kilogram; N/A = not applicable; q6h = every 6 hours

Table 80. Efficacy and Plasma Exposure of REL in Combination with Imipenem/Cilastatin in a Delayed Therapy *P. aeruginosa* Lung Infection Model (BLI-PA-14)

[1]Time post-infection (hr)	Dose (mg/kg IV as a 60 min infusion q6h for 24 hours)		Total Log10 CFU (SD)	Change Log10 CFU from 16.5 hr	Relebactam Plasma Concentration (uM at 2/3T)
	Imipenem	Relebactam			
16.5	N/A	N/A	4.71	N/A	N/A
24	N/A	N/A	7.92	+3.21	N/A
40	5	N/A	7.36	+2.65	N/A
40	5	20	5.20	[2]+0.49	32.77

1 Five animals per group
2 Not significantly different from CFU burden at start of therapy at 16.5 hours.

In Study PD040 REL was co-administered with a sub-inhibitory 5 mg/kg dose of IMI to determine the effect of REL on the ability of IMI to reduce lung bacterial burden. REL doses of 80, 40, 20, and 10 mg/kg were assessed in all but one study where doses of 40, 20, 10, and 5 mg/kg were tested. Nine *P. aeruginosa* and two *K. pneumoniae* isolates of varying susceptibility to imipenem were tested. Treatment was initiated at 17 hours after infectious challenge with *P. aeruginosa* or 3 hours after infectious challenge with *K. pneumoniae*. Combination treatment was delivered by 1-hour IV infusion every 6 hours. The PD results are summarized in Table 81 and Table 82.

Table 81. Outcome of Delayed Treatment Pulmonary Infection Model Experiments with *P. aeruginosa* (Study PD040)

Organism	Imipenem MIC	IMI/REL MIC	Imipenem Dose (mg/kg)	REL dose (mg/kg)	Log CFU Reduction from untreated control	Plasma REL and 2/3Y (uM)
CL5701	16	2	Pretreatment	Pretreatment	-2.51	N/A
			5 mg/kg	0 mg/kg	0.29	N/A
			0 mg/kg	80 mg/kg	0.54	177
			5 mg/kg	80 mg/kg	-1.97	150
			5 mg/kg	40 mg/kg	-1.64	90.3
			5 mg/kg	20 mg/kg	-1.88	33.9
			5 mg/kg	10 mg/kg	-1.87	21.0
CLB 24228	32	8	Pretreatment	Pretreatment	-3.19	N/A
			5 mg/kg	0 mg/kg	-0.19	N/A
			0 mg/kg	40 mg/kg	0.11	80.7

			5 mg/kg	40 mg/kg	-2.81	83.3
			5 mg/kg	20 mg/kg	-1.83	44.3
			5 mg/kg	10 mg/kg	-1.55	18.9
			5 mg/kg	5 mg/kg	-1.73	13.3
CLB 24228	32	8	Pretreatment	Pretreatment	-1.80	N/A
			5 mg/kg	0 mg/kg	0.48	N/A
			0 mg/kg	80 mg/kg	0.86	152
			5 mg/kg	80 mg/kg	-1.42	172
			5 mg/kg	40 mg/kg	-0.52	113
			5 mg/kg	20 mg/kg	-1.14	39.8
			5 mg/kg	10 mg/kg	-0.61	27
CLB 24228	32	8	Pretreatment	Pretreatment	-2.26	N/A
			5 mg/kg	0 mg/kg	0.23	N/A
			0 mg/kg	80 mg/kg	0.44	147
			5 mg/kg	80 mg/kg	-1.50	185
			5 mg/kg	40 mg/kg	-1.46	93.8
			5 mg/kg	20 mg/kg	-1.63	33.6
			5 mg/kg	10 mg/kg	-1.19	18.2
CLB 24385B	64	16	Pretreatment	Pretreatment	-2.38	N/A
			5 mg/kg	0 mg/kg	0.03	N/A
			0 mg/kg	80 mg/kg	0.96	174
			5 mg/kg	80 mg/kg	-1.30	137
			5 mg/kg	40 mg/kg	-1.38	102
			5 mg/kg	20 mg/kg	-1.31	38.7
			5 mg/kg	10 mg/kg	-1.34	23.8
CLB 24385B	64	16	Pretreatment	Pretreatment	-2.29	N/A
			5 mg/kg	0 mg/kg	-0.26	N/A
			0 mg/kg	80 mg/kg	-0.02	128
			5 mg/kg	80 mg/kg	-2.35	97.4
			5 mg/kg	40 mg/kg	-1.88	61.1
			5 mg/kg	20 mg/kg	-2.17	24.1
			5 mg/kg	10 mg/kg	-1.36	18.7
CLB 24385B	64	16	Pretreatment	Pretreatment	-3.12	N/A
			5 mg/kg	0 mg/kg	-0.97	N/A
			0 mg/kg	80 mg/kg	-0.28	200
			5 mg/kg	80 mg/kg	-1.86	174
			5 mg/kg	40 mg/kg	-2.45	103
			5 mg/kg	20 mg/kg	-2.00	31.5

			5 mg/kg	10 mg/kg	-2.30	21.5
CLB 24427	16	8	Pretreatment	Pretreatment	-1.96	N/A
			5 mg/kg	0 mg/kg	0.42	N/A
			0 mg/kg	80 mg/kg	-0.27	157
			5 mg/kg	80 mg/kg	-0.99	132
			5 mg/kg	40 mg/kg	0.58	106
			5 mg/kg	20 mg/kg	0.09	33.9
			5 mg/kg	10 mg/kg	-0.05	23.3
CLB 25005A	32	8	Pretreatment	Pretreatment	-3.34	N/A
			5 mg/kg	0 mg/kg	-0.04	N/A
			0 mg/kg	80 mg/kg	-0.81	136
			5 mg/kg	80 mg/kg	-2.46	116
			5 mg/kg	40 mg/kg	-1.58	88.2
			5 mg/kg	20 mg/kg	-2.10	31.0
			5 mg/kg	10 mg/kg	-2.08	19.5
CLB 25649	64	16	Pretreatment	Pretreatment	-3.11	N/A
			5 mg/kg	0 mg/kg	-1.29	N/A
			0 mg/kg	80 mg/kg	-0.49	144
			5 mg/kg	80 mg/kg	-2.85	98.0
			5 mg/kg	40 mg/kg	-2.84	93.6
			5 mg/kg	20 mg/kg	-1.32	21.6
			5 mg/kg	10 mg/kg	-1.04	28.2
CLB 25677	64	8	Pretreatment	Pretreatment	-2.94	N/A
			5 mg/kg	0 mg/kg	-1.62	N/A
			0 mg/kg	80 mg/kg	-0.39	137
			5 mg/kg	80 mg/kg	-2.18	150
			5 mg/kg	40 mg/kg	-2.86	100
			5 mg/kg	20 mg/kg	-1.80	29.8
			5 mg/kg	10 mg/kg	-0.79	23.1
CLB 25677	64	8	Pretreatment	Pretreatment	-3.82	N/A
			5 mg/kg	0 mg/kg	-0.69	N/A
			0 mg/kg	80 mg/kg	-0.19	177
			5 mg/kg	80 mg/kg	-2.14	158
			5 mg/kg	40 mg/kg	-2.04	101
			5 mg/kg	20 mg/kg	N/A	N/A
			5 mg/kg	10 mg/kg	-2.36	19.7
CLB 25893	64	16	Pretreatment	Pretreatment	-4.38	N/A
			5 mg/kg	0 mg/kg	-0.83	N/A

			0 mg/kg	80 mg/kg	-0.09	169
			5 mg/kg	80 mg/kg	-3.11	133
			5 mg/kg	40 mg/kg	-2.61	101
			5 mg/kg	20 mg/kg	-2.12	33.4
			5 mg/kg	10 mg/kg	-2.61	26.4
CLB 25893	64	16	Pretreatment	Pretreatment	-4.12	N/A
			5 mg/kg	0 mg/kg	-0.21	N/A
			0 mg/kg	80 mg/kg	0.21	108
			5 mg/kg	80 mg/kg	-2.54	118
			5 mg/kg	40 mg/kg	-2.58	69.0
			5 mg/kg	20 mg/kg	-2.79	26.4
			5 mg/kg	10 mg/kg	-2.68	17.2
CLB 26735	64	16	Pretreatment	Pretreatment	-3.10	N/A
			5 mg/kg	0 mg/kg	-1.16	N/A
			0 mg/kg	80 mg/kg	-0.26	502
			5 mg/kg	80 mg/kg	-2.54	166
			5 mg/kg	40 mg/kg	-2.28	81.3
			5 mg/kg	20 mg/kg	-0.77	34.3
			5 mg/kg	10 mg/kg	-0.37	30.0

Table 82.Outcome of Delayed Treatment Pulmonary Infection Model Experiments with *K. pneumoniae* (Study PD040)

Organism	Imipenem MIC	IMI/REL MIC	Imipenem Dose (mg/kg)	REL dose (mg/kg)	Log CFU Reduction from untreated control	Plasma REL and 2/3Y (uM)
487710	64	0.25	Pretreatment	Pretreatment	-3.15	N/A
			5 mg/kg	0 mg/kg	-0.96	N/A
			0 mg/kg	80 mg/kg	-1.38	122
			5 mg/kg	80 mg/kg	-3.61	257
			5 mg/kg	40 mg/kg	-3.44	102
			5 mg/kg	20 mg/kg	-3.37	44.3
			5 mg/kg	10 mg/kg	-3.06	26.4
487710	64	0.25	Pretreatment	Pretreatment	-2.12	N/A
			5 mg/kg	0 mg/kg	-0.58	N/A
			0 mg/kg	80 mg/kg	-0.62	99.5
			5 mg/kg	80 mg/kg	-3.64	155
			5 mg/kg	40 mg/kg	-2.98	88.9
			5 mg/kg	20 mg/kg	-2.19	30.0
			5 mg/kg	10 mg/kg	-1.32	21.8
515744	64	0.5	Pretreatment	Pretreatment	-2.68	N/A
			5 mg/kg	0 mg/kg	-0.77	N/A
			0 mg/kg	80 mg/kg	-0.75	91.3
			5 mg/kg	80 mg/kg	-2.21	172

			5 mg/kg	40 mg/kg	-2.43	85.2
			5 mg/kg	20 mg/kg	-1.08	27.7
			5 mg/kg	10 mg/kg	-0.91	18.0

The average REL 24-hour plasma exposure (AUC0-24 hr) that achieved stasis across all *P. aeruginosa* and *K. pneumoniae* strains in this experiment was approximately 40.5 mg*hour/L.

15.4.3 In Vivo Studies

Single and Multiple Ascending Dose Study

Study P001 was a 4-part, double-blind, randomized, placebo-controlled, sequential panel, rising single-dose study, and a sequential panel, multiple-rising-dose study to evaluate safety, tolerability and PK in healthy male subjects. All doses were administered to subjects in the fasted state. There was a minimum of a 7-day washout between periods.

- Part I (Panel A and B): Single dose REL ranging from 25 mg to 1150 mg. Each panel included 8 male subjects randomized to either active treatment (n=6) or placebo (n=2) per period, except for Period 4, where all subjects received a single IV dose of IMI (500 mg).
- Part II and Part III (Panels C, D, E, F, G, H, and I): Multiple IV doses of 500 mg IMI IV plus REL (q6h) daily for 7 consecutive days (n=6) or 500 mg IMI IV plus placebo to REL (q6h) daily for 7 consecutive days (n=2).
- Part IV (Panels J and K)**:** Multiple IV doses of 500-mg REL and 500-mg IMI IV, q6h daily, for 14 consecutive days (n=24) or placebo for REL and 500-mg IMI IV, q6h daily for 14 consecutive days (n=8).

Results indicate a dose-proportional increase in REL $AUC_{0-\infty}$ and C_{max} at the dose range of 25 to 1150 mg. REL is almost completely excreted through urine with fraction of dose excreted through urine (fe) ranging from ranging from 94.7% to 100% over a 24-hour period following single dose administration and 89.2% to 99.5% over a 6 hour period on Day 7 for multiple doses. The renal clearance (CLr) and fe are similar across the entire dose range (25 mg to 1150 mg). The REL CLr and fe are similar when REL is administered with and without IMI IV. IMI® IV. The PK parameters from Parts II and III are summarized in

Table 83. Because of a very short half-life, when REL is administered q6h for multiple days, AUC_{0-6hr} reaches steady state within 1 day of dosing.

Table 83. REL PK following multiple IV doses of REL plus Imipenem IV 500 mg Every 6 Hours for 7 Days (Part II and III) – Geo Mean (90% Confidence interval); T1/2- Geo Mean (% Geo CV)

REL Dose plus 500 mg IMI	50 mg Day 1	50 mg Day 7	125 mg Day 1	125 mg Day 7	250 mg Day 1	250 mg Day 7	375 mg Day 1	375 mg Day 7	500 mg Day 1	500 mg Day 7	625 mg Day 1	625 mg Day 7
$AUC_{0\text{-}6}$ (μM*hr)	17.5 (15.7, 19.5)	15.6 (13.9, 17.4)	43.0 (39.9, 46.5)	42.5 (39.4, 45.9)	78.2 (70.1, 87.1)	81.6 (73.2, 91.0)	104 (93.5, 116)	120 (107, 134)	161 (144, 179)	167 (149, 186)	186 (167, 207)	194 (174, 216)
Cmax (μM)	9.80 (8.43, 11.4)	9.02 (7.69, 10.6)	25.4 (22.9, 28.3)	26.5 (23.8, 29.4)	46.5 (40.1, 54.0)	48.3 (41.5, 56.0)	58.4 (50.2, 67.8)	69.6 (59.9, 80.8)	95.8 (82.5, 111)	101 (86.8, 117)	116 (100, 135)	114 (98.3, 133)
$T_{1/2}$ (hr)	1.64 (5.2)	1.42 (8.6)	1.44 (13.9)	1.40 (12.9)	1.63 (8.2)	1.66 (14.2)	1.48 (9.5)	1.86 (13.3)	1.56 (16.0)	1.69 (11.9)	1.48 (12.5)	1.73 (10.7)

Drug-drug Interaction Studies

Interaction between all three components (Study PN001): In Study PN001, the interaction among REL, IMI and CIL were evaluated in healthy male volunteers. The results are summarized in Table 84 and Table 85, indicating that there are no clinically relevant drug interactions among REL, IMI and CIL.

Table 84. PK parameters of REL following a single dose administration with and without 500 mg IMI/CIL IV. Results reported as GM (95% CI)

REL Dose	50 mg		500 mg	
	(-) IMI/CIL IV	(+) IMI/CIL IV	(-) IMI/CIL IV	(+) IMI/CIL IV
$AUC_{0\text{-}\infty}$ (μM*hr)	15.9 (14.3, 17.6)	16.8 (15.1, 18.7)	173 (155, 192)	176 (158, 195)
Cmax (μM)	9.03 (7.86, 10.4)	9.08 (7.91, 10.4)	98.1 (85.4, 113)	91.2 (79.5, 105)

Table 85. PK parameters of IMI and CIL following administration of 500 mg IMI/CIL IV with and without 500 mg REL. Results reported as GM (95% CI)

	Imipenem		Cilastatin	
	(-) REL	(+)REL	(-) REL	(+)REL
$AUC_{0\text{-}\infty}$ (μM*hr)	141 (126, 156)	145 (129, 162)	113 (102,126)	112 (101, 124)
Cmax (μM)	104 (95.8, 113)	102 (92.7, 112)	100 (86.3, 116)	102 (87, 118)

Study PN019: Effect of Probenecid (Renal OAT1 and OAT3 Inhibitor)

Study PN019 was an open-label, randomized, 2-period, crossover study in 14 healthy adult male and female subjects.

- Treatment A: A single IV dose of IMI/ REL (500 mg IMI/500 mg CIL/250 mg REL)
- Treatment B: A single 1-gram oral dose of probenecid administered 1 hour prior to a single IV dose of IMI/REL (500 mg IMI/500 mg CIL/250 mg REL)

There was a washout of 7 days between the start of each REL infusion. Subjects fasted overnight for at least 8 hours prior to each IMI/REL administration and continued to fast for at least 4 hours following the start of IMI/REL infusion. The geometric mean ratios of REL and IMI PK parameters between the treatment groups are summarized in Table 86. There was no substantial difference in terminal half-lives of REL and IMI in the two treatment groups.

Table 86. Geometric Mean Ratio of REL and IMI PK Parameters Following Administration of a Single IV Infusion of IMI/REL With and Without a Single Oral Dose of 1 g Probenecid in Healthy Adult Subjects

	Geometric mean ratio (90% confidence interval)	
	REL	IMI
$AUC_{0-\infty}$	1.24 (1.19, 1.28)	1.16 (1.13, 1.20)
Cmax	1.06 (1.00, 1.12)	1.07 (1.01, 1.13)
CLr	0.81 (0.78, 0.84)	0.86 (0.83, 0.89)

CLr = renal clearance

Intrinsic Factors

Gender and Age

Study P002 was a randomized, double-blind, placebo-controlled study in healthy elderly (65 to 75 years of age with normal renal function for their age) male subjects (Panel A; n=8), healthy elderly female subjects (Panel B; n=8), and healthy young female subjects (Panel C; n=8). In each panel, subjects received a single IV dose of 125 mg REL (n=6) or placebo (placebo) to REL coadministered with 500 mg IMI IV (n=2) as a 30-minute infusion. Data from this study were compared with historical control data from healthy young male subjects (Study PN001).

Table 87. Between-population Comparison of REL PK [Geometric Mean (CI)]

	Elderly female vs elderly male	Young female vs young male	Elderly male vs. young male	Elderly female vs. young female
AUC_{0-24} (μM*hr)	1.24 (1.03, 1.49)	1.16 (0.97, 1.40)	1.35 (1.12, 1.62)	1.43 (1.19, 1.73)
CL (mL/min)	0.81 (0.67, 0.97)	0.86 (0.71, 1.03)	0.74 (0.62, 0.89)	0.70 (0.58, 0.84)
Cmax (μM)	1.59 (1.25, 2.03)	1.35 (1.06, 1.73)	1.01 (0.79, 1.29)	1.19 (0.93, 1.52)

The mean REL plasma $AUC_{0-\infty}$ were slightly higher in both young and elderly female groups when compared to male subjects in the same age groups, increasing 16% and 24%, respectively. Elderly groups had higher mean exposures than young subjects of the same gender, increasing by 35% and 43%, respectively. However, these four patient populations were included in the Applicant's safety analysis and no notable differences in adverse events were observed. Thus, dosage adjustment of REL is not necessary for age or gender.

Race

Study MK7655-012 was a randomized, double-blind, placebo-controlled, single and multiple IV dose trial to assess the safety, tolerability and PK of REL and IMI in healthy male Japanese subjects (N=19). In Periods 1-3, subjects received single IV doses of 125-, 250- and 500-mg REL co-infused with 500-mg IMI (n= 6) or placebo (n=2). In Periods 4 and 5, subjects received multiple doses of 250 and 500 mg of REL co-infused with 500-mg IMI (n= 6) or placebo (n=2) every 6 hours for 14 days in each period. There were 2 alternating panels of subjects. Subjects in Panel A participated in Periods 1, 3 and 5; subjects in Panel B participated in Periods 2 and 4. PK parameters for REL and IMI at the clinically relevant doses are highlighted in Table **88**.

Table 88. Relebactam and Imipenem PK Parameters Following Single IV Infusion of 250 mg Relebactam Coadministered with 500 mg IMI/CIL to Healthy Japanese Male Subjects

	REL 250 mg	IMI 500 mg
$AUC_{0-\infty}$ (µmol•hr/L)	85.0 (76.9, 94.1)	185 (172, 199)
Cmax (µmol/L)	43.1 (38.8, 47.9)	129 (116, 144)
$t_{1/2}$ (hr)	1.70 (11.2)	1.11 (9.87)

An exploratory analysis of similarity of single and multiple dose PK parameters for REL between healthy Japanese (Study PN012) and non-Japanese (Study PN001) male subjects was performed. The distributions of exposure overlapped and the GMRs (Japanese/non-Japanese) and 90% CIs were 1.04 (0.96, 1.12) for AUC0-∞, 1.04 (0.95, 1.13) for AUC_{0-6hr}, and 0.96 (0.87, 1.05) to 1.03 (0.93, 1.15) for Cmax, suggesting that the PK profile of REL was comparable between Japanese and non-Japanese.

Renal Impairment

P005 was a 2-part study. Part I was an open-label, single-dose study comparing the PK of a 125-mg dose of REL dosed in combination with 250-mg IMI IV in subjects with impaired renal function. IMI and REL were administered as separate vials and infused concurrently. This study consisted of 8 panels (Panels A to H) and included six (6) subjects in each of the following renal impairment groups: mild (eGFR >50 to < 80 mL/min/1.73m^2), moderate (eGFR >30 to < 50 mL/min/1.73m$^{2)}$, severe (eGFR <30 mL/min/1.73m^2) and ESRD requiring dialysis. Subjects with ESRD on hemodialysis received a single dose of each study drug immediately following their normally scheduled hemodialysis (post-dialysis). The same subjects with ESRD then received an additional single dose of the study drugs 30 minutes prior to their normally scheduled hemodialysis (pre-dialysis).

eGFR was estimated based on the modification of diet in renal disease (MDRD) equation. Subjects with renal impairment were compared to age-, gender-, and BMI-matched subjects with normal renal function.

Table 89 and Table 90 summarize the pharmacokinetic parameters of REL and IMI, respectively, in subjects with varying degrees of renal impairment.

Table 89. Summary of REL PK Following Administration of a Single IV Dose of REL (125 mg) Coadministered with IMI IV (250 mg) in Subjects with Impaired Renal Function

	Renal Impairment Geo Mean (95% CI)	Healthy Controls Geo Mean (95% CI)	Renal Impairment/Healthy Control Geo Mean Ratio (90% CI)
Mild Renal Insufficiency			
$AUC_{0-\infty}$ (μM*hr)	73.5 (50.0, 108)	45 (32.4, 62.6)	1.63 (1.12, 2.39)
Cmax ((μM)	22.4 (13.0, 38.7)	20.4 (12.8, 32.7)	1.10 (0.64, 1.88)
CLpred (mL/min)	81.3 (55.3, 119)	113 (95.5, 185)	0.61 (0.42, 0.90)
$T_{1/2}$ (hr) geo mean (%CV)	2.63 (26.4)	1.75 (16.6)	
Fe (%)	79.4 (7.4)	83.3 (17.6)	
CLr (mL/min)	69.8 (16.5)	118 (19.8)	
Moderate Renal Insufficiency			
$AUC_{0-\infty}$ (μM*hr)	115 (79.8, 165)	52.3 (27.7, 72.7)	2.19 (1.51, 3.18)
Cmax ((μM)	23.5 (14, 39.4)	22.5 (14.1, 35.9)	1.04 (0.62, 1.77)
CLpred (mL/min)	52.1 (36.2, 74.9)	114 (82.3, 159)	0.46 (0.31, 0.66)
$T_{1/2}$ (hr) geo mean (%CV)	4.51 (25.7)	2.10 (31.0)	
Fe (%)	60.3 (28.9)	86.2 (15.3)	
CLr (mL/min)	38.4 (28.8)	110 (36)	
Severe Renal Insufficiency			
$AUC_{0-\infty}$ (μM*hr)	236 (171, 325)	48.5 (35.2, 66.4)	4.87 (3.37, 7.04)
Cmax ((μM)	23.6 (15.0, 37.2)	18.1 (11.6, 28.4)	1.30 (0.77, 2.20)
CLpred (mL/min)	25.3 (18.4, 34.9)	123 (90, 169)	0.21 (0.14, 0.30)
$T_{1/2}$ (hr) geo mean (%CV)	8.65 (31.0)	2.0 (10.4)	
Fe (%)	59.1 (20.7)	81.8 (10.1)	
CLr (mL/min)	22.3 (47.2)	107 (20.9)	
End Stage Renal Disease (post-dialysis)			
$AUC_{0-\infty}$ (μM*hr)	414 (280, 612)	44.5 (29.1, 67.9)	9.32 (6.45, 13.46)
Cmax ((μM)	53.1 (30.7, 91.9)	22.7 (12.5, 41.0)	2.34 (1.39, 3.96)
CLpred (mL/min)	14.4 (9.77, 21.3)	135 (88.1, 206)	0.11 (0.79, 1.16)
$T_{1/2}$ (hr) geo mean (%CV)	15.6 (103.1)	1.79 (13.9)	
End Stage Renal Disease (pre-dialysis)			
$AUC_{0-\infty}$ (μM*hr)	78.0 (50.3, 121)	44.5 (29.1, 67.9)	1.76 (1.20, 2.58)
Cmax ((μM)	19.3 (11.2, 33.4)	22.7 (12.5, 41.0)	0.85 (0.50, 1.44)
CLpred (mL/min)	76.6 (49.4, 119)	135 (88.1, 206)	0.57 (0.39, 0.84)
$T_{1/2}$ (hr) geo mean (%CV)	10.5 (100.6)	13.9	

AUC = area under the curve; CI = confidence interval; IMI= imipenem; REL = relebactam; Geo = geometric; PK = pharmacokinetic; fe = fraction of dose excreted unchanged in urine; CLr = renal clearance. Patients with end stage renal disease did not have urine collection given the limitations of producing urine

Table 90. Summary of IMI PK Following Administration of a Single IV Dose of REL (125 mg) Coadministered with Imipenem IV (250 mg) in Subjects with Impaired Renal Function

	Renal Impairment Geo Mean (95% CI)	Healthy Controls Geo Mean (95% CI)	Renal Impairment/Healthy Control Geo Mean Ratio (90% CI)
Mild Renal Insufficiency			
$AUC_{0-\infty}$ (μM*hr)	77.3 (58.9, 101)	55.0 (43.5, 69.5)	1.41 (1.07, 1.84)
Cmax ((μM)	40.7 (22.7, 73.2)	35.3 (21.3, 58.5)	1.15 (0.65, 2.06)
CLpred (mL/min)	180 (137, 236)	253 (200, 320)	0.71 (0.54, 0.93)
$T_{1/2}$ (hr) geo mean (%CV)	1.54 (15.2)	1.24 (10.8)	
Fe (%)	45.0 (12)	46.5 (25.3)	
CLr (mL/min)	75.0 (14.6)	115 (18.4)	
Moderate Renal Insufficiency			
$AUC_{0-\infty}$ (μM*hr)	101 (77.9, 130)	66 (52.2, 83.3)	1.53 (1.17, 1.99)
Cmax ((μM)	45.6 (26.2, 79.5)	42.6 (25.8, 70.4)	1.07 (0.61, 1.89)
CLpred (mL/min)	138 (107, 179)	211 (167, 266)	0.65 (0.50, 0.85)
$T_{1/2}$ (hr) geo mean (%CV)	2.18 (12.8)	1.40 (21.1)	
Fe (%)	28.9 (38.4)	51.0 (14.6)	
CLr (mL/min)	41.1 (23.8)	109 (29.2)	
Severe Renal Insufficiency			
$AUC_{0-\infty}$ (μM*hr)	160 (127, 210)	63.8 (51.0, 79.9)	2.51 (1.93, 3.26)
Cmax ((μM)	46.9 (28.7, 76.5)	35.5 (21.9, 57.6)	1.32 (0.75, 2.32)
CLpred (mL/min)	87.0 (69.4, 109)	218 (174, 273)	0.40 (0.31, 0.52)
$T_{1/2}$ (hr) geo mean (%CV)	2.78 (11.9)	1.32 (5.8)	
Fe (%)	20.2 (17.1)	48.9 (11.6)	
CLr (mL/min)	17.4 (44.7)	104 (10.5)	
End Stage Renal Disease (post-dialysis)			
$AUC_{0-\infty}$ (μM*hr)	223 (169, 293)	71.8 (53.4, 96.5)	3.10 (2.39, 4.03)
Cmax ((μM)	103 (57.1, 186)	41.8 (22.1, 79.1)	2.46 (1.40, 4.33)
CLpred (mL/min)	62.5 (47.5, 82.1)	194 (144, 261)	0.32 (0.25, 0.42)
$T_{1/2}$ (hr) geo mean (%CV)	3.24 (18.7)	1.21 (13.7)	
End Stage Renal Disease (pre-dialysis)			
$AUC_{0-\infty}$ (μM*hr)	71.2 (54.2, 93.6)	71.8 (53.4, 96.5)	0.99 (0.76, 1.29)
Cmax ((μM)	35.9 (19.9, 64.7)	41.8 (22.1, 79.1)	0.86 (0.49, 1.51)
CLpred (mL/min)	195 (149, 257)	194 (244, 261)	1.01 (0.78, 1.31)
$T_{1/2}$ (hr) geo mean (%CV)	3.20 (47.8)	1.21 (13.7)	

AUC = area under the curve; CI = confidence interval; IMI= imipenem; REL = relebactam; Geo = geometric; PK = pharmacokinetic; fe = fraction of dose excreted unchanged in urine; CLr = renal clearance. Patients with end stage renal disease did not have urine collection given the limitations of producing urine

Relative to matched healthy controls, the GMRs of $AUC_{0-\infty}$ for IMI vs. REL were similar in subjects with mild (1.41 vs. 1.63) and moderate (1.53 vs. 2.19) renal impairment. However, the GMRs of $AUC_{0-\infty}$ of imipenem and REL were substantially different in subjects with severe renal impairment (i.e., 4.87 for REL vs. 2.51 for IMI, indicating that a fixed dosage adjustment for IMI and REL for patients with severe renal impairment may not be able to provide those patients

with comparable exposures of both drugs. The fraction of dose excreted unchanged in urine (fe) decreased with degree of renal impairment for both IMI and REL. Both IMI and REL were effectively cleared from plasma by HD, with extraction coefficients of 66 % to 87 % for IMI, 46 % to 56 % for CIL and 67 % to 87 % for REL.

There were no serious adverse events (SAEs) and no deaths observed in this study.

15.4.4 Pharmacometrics Review

1. Pharmacometrics Review

1.1. Population PK analyses

1.1.1. Introduction

The applicant developed a population pharmacokinetic model using pooled data from seven phase 1 (PN001, PN002, P005, PN007, PN009, PN012 and PN019), two studies (PN003 and PN004), one each in cUTI and cIAI and one study (PN013) in imipenem-resistant organisms. The objectives of the applicant's population PK analyses were to:

i. Estimate the population pharmacokinetic parameters of imipenem and relebactam following intravenous infusion administration in an adult population, including healthy adult volunteers and adult patients with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) or hospital-acquired / ventilator associated bacterial pneumonia (HABP/VABP).
ii. Evaluate patient demographics and other covariates influencing the population pharmacokinetics of imipenem and relebactam, with interest on the impact of CrCL, body weight, age, gender and health.
iii. Determine the probability of target attainment (PTA) using simulations to support dose regimen selection in normal and renally impaired patients, using the developed population-PK model.
iv. Derive post hoc individual parameter estimates of patients in the study PN013 to facilitate Exposure Response analysis.

This review will focus on the adequacy of the recommended imipenem and rele bactam dose and whether the labelling language is supported by the applicant's findings on the influence of intrinsic and extrinsic covariates on the PK parameters.

1.1.2. Methods

Data

Study PN001 was a single and multiple dose study in healthy young male volunteers. The study was conducted in four parts. Part I of the study had two panels and six periods: in period 1, 2, 3, and 5, subjects received either a placebo or one of the single ascending doses of relebactam (Panel A: 25, 50, 125, 250; panel B: 250, 500, 1000, 1150). In period 4, all subjects received imipenem 500 mg while in period 6 subjects received both relebactam and imipenem (Panel A: 50 mg/500 mg relebactam/imipenem; Panel B; 500 mg/500 mg relebactam/imipenem). Blood samples for quantification of relebactam, imipenem and cilastatin plasma concentrations were collected pre-dose and at 0-, 5-, 15-, 30-minutes, 1-, 1.5-, 2-, 3-, 4.5-, 6-, 8-, 10-, and 14- hours after dose.

Part II of the study consisted of four sequential, 7-days dosing panels for imipenem 500 mg/relebactam. Relebactam (n=6) or matched placebo (n=2) were given in the ascending order of 125 mg, 250 mg, 500 mg, and 1000 mg in panel C, D, E, and F respectively. A washout period of 7 days was allowed between the panels.
Part III consisted of three sequential, 7-days dosing panels for imipenem 500 mg/relebactam. Relebactam was administered in ascending order of 375 mg, 500 mg, and 625 mg in panel G, H, and I respectively. A washout period of 14 days was allowed between the panels.
In both part II and III imipenem and relebactam were administered every 6 hours daily for 7 days. Blood samples for quantification of imipenem, relebactam and cilastatin levels were collected at pre-dose, 5-, 15-, 30-, 45-minutes, 1-, 1.5-, 2-, 3-, 4.5-, 6-, 8, 12-, and 18-hours post dose on day 1. Blood samples were also collected on day 7 at pre-dose, 5-, 15-, 30-, 45-minutes, 1-, 1.5-. 2-, 3-, 4.5-, 6-, 8-, 10-, and 14-hours post-dose. Additional blood samples were collected pre-dose to the first daily infusion on days 2, 4, and 6 in all the panels.
Part IV consisted of two sequential dosing panel. In both panel 16 subjects were randomized to receive either 500 mg/ 500 mg imipenem/relebactam (n = 12) or 500 mg/ 0 mg imipenem/relebactam (placebo) every 6 hours daily, for 14 consecutive days. Blood samples for quantification of imipenem, relebactam and cilastatin levels were collected at pre-dose, 5-, 15-, 30-, 45-minutes, 1-, 1.5-, 2-, 3-, 4.5-, and 6-hours post dose on day 1. Blood samples were also collected on day 14 at pre-dose, 5-, 15-, 30-, 45- minutes, 1-, 1.5-. 2-, 3-, 4.5-, 6-, 8-, 10-, and 14-hours post-dose. Additional blood samples were collected pre-dose to the first daily infusion on days 4, 8, and 12 in all the panels.
Study PN002 was a randomized, double blind, placebo-controlled study in healthy elderly male (60-75 years of age, panel A), healthy elderly female (60 – 75 years of age, panel B) and healthy young female (18 – 45 years of age, panel C) subjects. In each panel six subjects received 500 mg/125 mg of imipenem/relebactam and two subjects received 500 mg imipenem and placebo. Blood samples for quantification of relebactam, imipenem and cilastatin plasma concentrations were collected pre-dose and at 5-, 15-, 30-, 45- minutes, 1-, 1.5-, 2-, 3-, 4.5-, 6-, 8-, 10-, and 14-hours after dose
Study P005 was an open label, single dose study to investigate the effect of varying degrees of renal insufficiency on pharmacokinetics of relebactam. In part I, subjects with impaired renal function (n = 24) and healthy matched controls (n = 24) received single doses of imipenem 250 mg/relebactam 125 mg. Blood samples for quantification of relebactam, imipenem and cilastatin plasma concentrations were collected pre-dose and at 5-, 15-, 30-, 45- minutes, 1-, 1.5-, 2-, 3-, 4.5-, 6-, 8-, 10-, and 14- hours after dose.
Study PN007 was an open label study to evaluate the pharmacokinetics of relebactam and imipenem in the lungs after multiple doses in health young male or female subjects. All subjects received 5 doses of imipenem 500 mg/relebactam 250 mg administered every 6 hours. After the last dose each subject underwent a bronchoscopy with bronchioalveolar lavage to obtain epithelial lining fluid and alveolar cells for analysis. Bronchoscopies were performed at pre-dose and at 0, 0.5, 1, 1.5, and 3 hours post-last-dose. Blood samples for quantification of relebactam, imipenem and cilastatin plasma concentrations were collected prior to dose 1 and dose 5 and at bronchoscopy time points.

Study PN009 was a single dose, double blind, randomized, placebo and positive controlled study to assess QTc interval prolongation potential of relebactam. On 3 different occasions, each subject received 1150 mg of relebactam; 400 mg of moxifloxacin; or relebactam matching placebo. A washout period of 4 days was allowed between the occasions. Blood samples for quantification of relebactam plasma concentrations were collected pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours after dose.

Study PN012 was a randomized, placebo controlled, double-blind, single and multiple ascending dose study of imipenem/relebactam in healthy Japanese male subjects. In period 1 to 3, a set of subjects (n=6) received single escalating doses of 125, 250, and 500 mg of relebactam + imipenem 500 mg or placebo (n=2) in each period. In period 4 and 5, another set of subjects (n=6) received escalating doses of 250 and 500mg of relebactam + imipenem 500mg or placebo (n=2). Blood samples for quantification of relebactam, imipenem and cilastatin plasma concentrations were collected pre-dose and at 5-, 15-, 30-, 45- minutes, 1-, 1.5-, 2-, 3-, 4.5-, 6-, 8-, 10-, and 14- hours after dose.

Study PN019 was an open label, randomized, 2-period, crossover study in 14 healthy adult subjects to examine safety and pharmacokinetic interaction between probenecid and relebactam. On day 1 of each period subjects received either a single IV dose of imipenem 500 mg/ relebactam 250 mg or a single oral dose of probenecid (1000 mg) administered 1 hour prior to a single IV dose of relebactam. Blood for relebactam and imipenem pharmacokinetics were collected at pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4.5, 6, 8, 10, 12, 16, and 24 hours after dose.

Study PN003 was a study in patients with complicated urinary tract infections (cUTI). Subjects were randomized to one of the following doses: imipenem 500 mg/relebactam 250 mg (n =99); imipenem 500 mg/relebactam 125 mg (n =99); and imipenem 500 mg/placebo (n =100). Blood samples for quantification of relebactam and imipenem plasma levels were collected at screening and at 30 minutes and 4 hours post-dose on day 1 of treatment initiation. For subjects who were switched IV therapy due to imipenem resistance development, additional blood samples were collected on day 3 (30 minutes and 4 hours post-infusion).

Study PN004 was a study in patients with complicated intra-abdominal infections (cIAI). Subjects were randomized to one of the following doses: imipenem 500 mg/relebactam 250 mg (n =117); imipenem 500 mg/relebactam 125 mg (n =114); and imipenem 500 mg/placebo (n =116). Blood samples for pharmacokinetic evaluations were collected at screening and at pre-dose, 30-minutes, and 4 hours post-dose on day 1. For subjects who switched therapy due to imipenem resistance or unfavorable clinical response, additional blood samples were collected on day 3.

Study PN013 was a study in patients with multi-drug resistant infections including cUTI, cIAI, and HABPV/VABP. Subjects were randomized to two treatment arms and received either relebactam or colistin based imipenem/cilastatin treatment. In the relebactam arm (n = 31), subjects were administered imipenem 500 mg/ relebactam 250 mg every 6 hours while in the colistin arm (n=16), subjects were administered imipenem 500 mg every 6 hours and loading dose of colistimethane sodium (CMS) at initiation followed by CMS 300 mg every 12 hours. Treatment was for a minimum duration of 5 days for subjects with cUTI and cIAI, and 7 days for subjects HABP/VABP. Treatment duration could be extended to a maximum of 21 days. Blood

samples for quantification of relebactam and imipenem plasma levels were collected at screening and at 30 minutes and 4 hours post-dose on day 1 of treatment initiation.

Missing data

Dosing times: Where dosing times were missing, samples were excluded from the analysis.
BQL samples: Data below limit of quantification were excluded from the analysis.
Observation times: records with missing sampling times were excluded from the analysis.
Covariate values: There were no missing categorical covariates. For creatinine clearance (CRCL) and body weight (WT), less than 15% of subjects had missing information and these were imputed by median values.

Outliers

Exploratory pharmacokinetic data plots did not identify sufficiently anomalous concentrations to justify exclusion as outliers. However, some subjects with data from PN003 and PN004 were identified whose end of infusion concentrations were lower than those observed at 4-hour post-dose. These subjects were excluded from the analysis.
During population PK model development, data points with absolute CWRES > 6 were removed to test for sensitivity of PK parameters to those data points. These datapoints were subsequently excluded from further analysis.
Quantifiable pre-dose concentrations were also excluded from the analysis.

Population PK modeling

The applicant developed population pharmacokinetic models for both imipenem and relebactam using NONMEM version 7.3.0 and PsN version 4.7.0. Post-processing of NONMEM results was done in R version 3.5.1. The models for imipenem and relebactam were developed separately through several similar steps. The first step involved development of structural and stochastic models using data from phase 1 studies. At the first stage the applicant found that a 2-compartment model was a best fit for observed imipenem and relebactam pharmacokinetic data. Structural model parameters were formulated in terms of clearance from central compartment (CL), volume of the central compartment (V1), inter-compartment clearance (Q), and volume of the peripheral compartment (V2). Stochastic model parameters included between subject variabilities (BSV) on CL, V1, and V3. A proportional residual error structure provided a better fit than alternative residual error models.
The second stage involved identification of covariates influencing different structural model parameters. At this stage data from PN003 and PN004 were included in the analysis. The applicant employed step-wise covariate model building approach to identify clinically meaningful and statistically significant covariates. Forward covariate search included covariates that were associated with 6.63 points decrease (at DF = 1) in model objective function value (OFV). Backward step removed covariates from the model if OFV increased by less than 10.83 upon removal of such covariates. Covariates investigated for influence on CL included CRCL, WT, health status (HLTH), age, sex, and race. Covariates tested on V1 and V2 were: WT, age, sex, and race. WT was tested on Q. CRCL was calculated from serum creatinine using the Cockcroft – Gault equation. After completion of covariate analysis, the applicant included covariance structure between CL and V1 leading to further improved fit to observed data for both relebactam and imipenem models.

The final model was qualified through, diagnostic goodness of fit plots, bootstrap analysis and visual predictive check.

1.1.3. Results

Pharmacokinetic data were available from a total of 855 subjects (815 with imipenem levels and 649 with relebactam levels) providing 4454 and 4814 quantifiable plasma concentrations of imipenem and relebactam respectively.

Categorical covariates

	Number of Subjects	Percentage of Subjects
Creatinine Clearance Category		
CrCL < 15 mL/min	5	0.6
CrCL mL/min ≥15 and < 30	9	1.1
CrCL mL/min ≥ 30 and < 60	70	8.2
CrCL mL/min ≥ 60 and < 90	199	23.4
CrCL mL/min ≥ 90 and < 150	439	51.5
CrCL mL/min ≥ 150 and < 180	103	12.1
CrCL mL/min ≥ 180 and < 210	18	2.1
CrCL mL/min ≥ 210 and < 250	4	0.5
CrCL mL/min ≥ 250	5	0.6
Gender		
Male (MALE = 1)	519	60.7
Female (FEMALE = 0)	336	39.3
Healthy (HLTH)		
Healthy Volunteer (HLTH = 1)	231	27.0
Patients (HLTH = 0)	624	73.0
Race		
White (RACE = 1)	739	86.4
Black (RACE = 2)	32	3.7
Asian (RACE = 3)	44	5.2
Other (RACE = 4)	40	4.7

Total number of subjects = 855 (815 subjects with imipenem measurements and 649 subjects with relebactam measurements). For the CrCL categories statistics 3 individuals had missing CrCL values and therefore calculated statistics are shown for the remaining n=852 individuals

shows the descriptive statistics of covariates which were investigated for influence on PK parameters. Table 91 shows the final parameter estimates for relebactam and imipenem models. **Error! Reference source not found.** and Figure 21 show the goodness-of-fit plots for imipenem and relebactam final models respectively. Figure 23 and Figure 22 show the dose-normalized visual predictive check of the final models.

Figure 19. Descriptive statistics of subjects-characteristics investigated for influence on PK parameters

Continuous covariates

	Mean	SD	Q1	Median	Q3	Range	N Missing
Creatinine Clearance (mL/min)	109.4	41.4	80.9	109.1	134.9	7.9 - 406.3	3
Weight (kg)	77.1	16.1	65.3	76.0	85.4	39.2 - 180.0	1
Age (years)	49.7	18.2	34.0	51.0	65.0	18.0 - 90.0	0

Total number of subjects = 855 (815 subjects with imipenem and 649 subjects with relebactam measurements)

Source: Merck-7655A/Analysis/r-scripts/analysis-report-covariate-summary.R

Categorical covariates

	Number of Subjects	Percentage of Subjects
Creatinine Clearance Category		
CrCL < 15 mL/min	5	0.6
CrCL mL/min ≥15 and < 30	9	1.1
CrCL mL/min ≥ 30 and < 60	70	8.2
CrCL mL/min ≥ 60 and < 90	199	23.4
CrCL mL/min ≥ 90 and < 150	439	51.5
CrCL mL/min ≥ 150 and < 180	103	12.1
CrCL mL/min ≥ 180 and < 210	18	2.1
CrCL mL/min ≥ 210 and < 250	4	0.5
CrCL mL/min ≥ 250	5	0.6
Gender		
Male (MALE = 1)	519	60.7
Female (FEMALE = 0)	336	39.3
Healthy (HLTH)		
Healthy Volunteer (HLTH = 1)	231	27.0
Patients (HLTH = 0)	624	73.0
Race		
White (RACE = 1)	739	86.4
Black (RACE = 2)	32	3.7
Asian (RACE = 3)	44	5.2
Other (RACE = 4)	40	4.7

Total number of subjects = 855 (815 subjects with imipenem measurements and 649 subjects with relebactam measurements). For the CrCL categories statistics 3 individuals had missing CrCL values and therefore calculated statistics are shown for the remaining n=852 individuals

Source: Applicant's population pharmacokinetic analysis report; page 49 of 320.

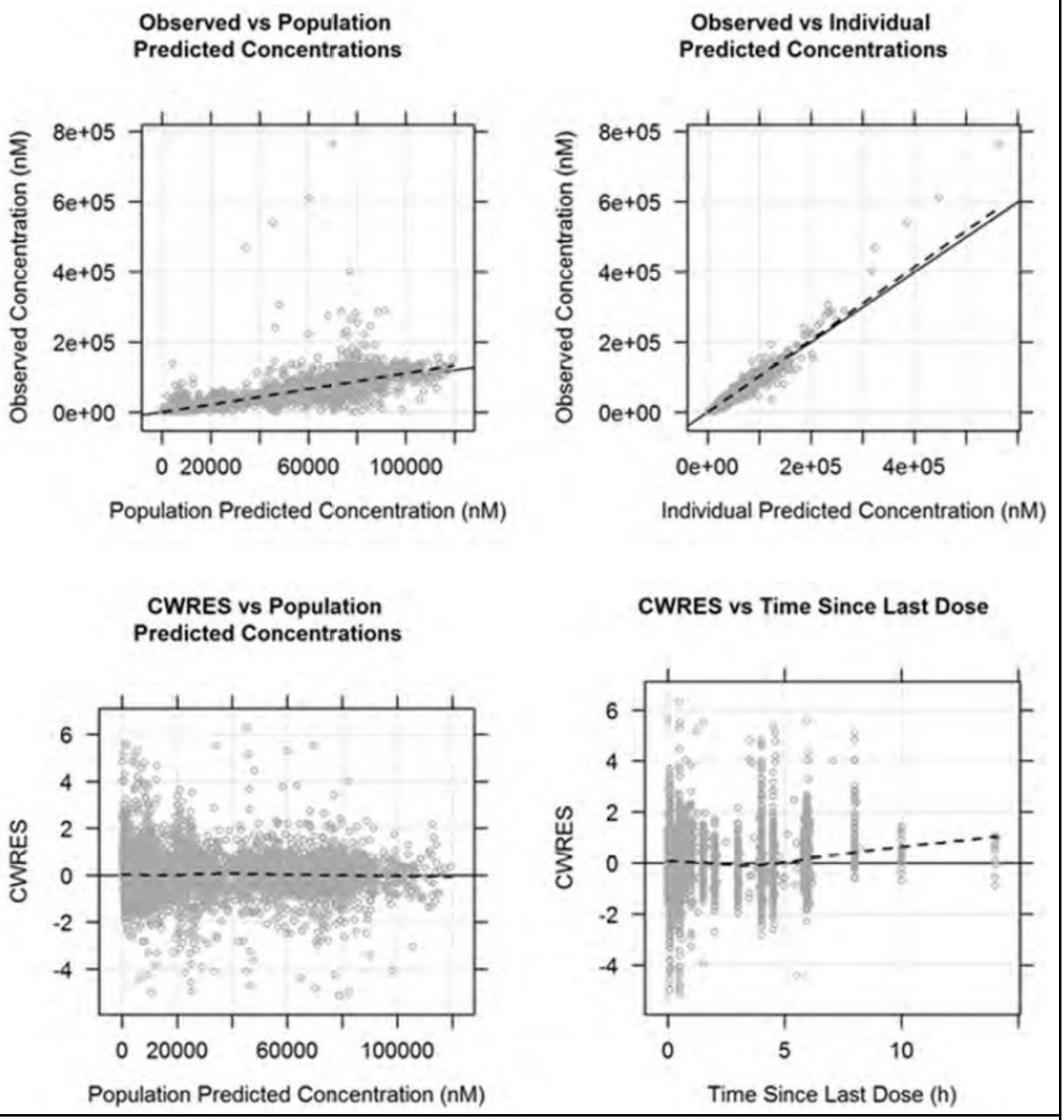
Table 91. Final Imipenem and Relebactam Model Parameter Estimates

	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

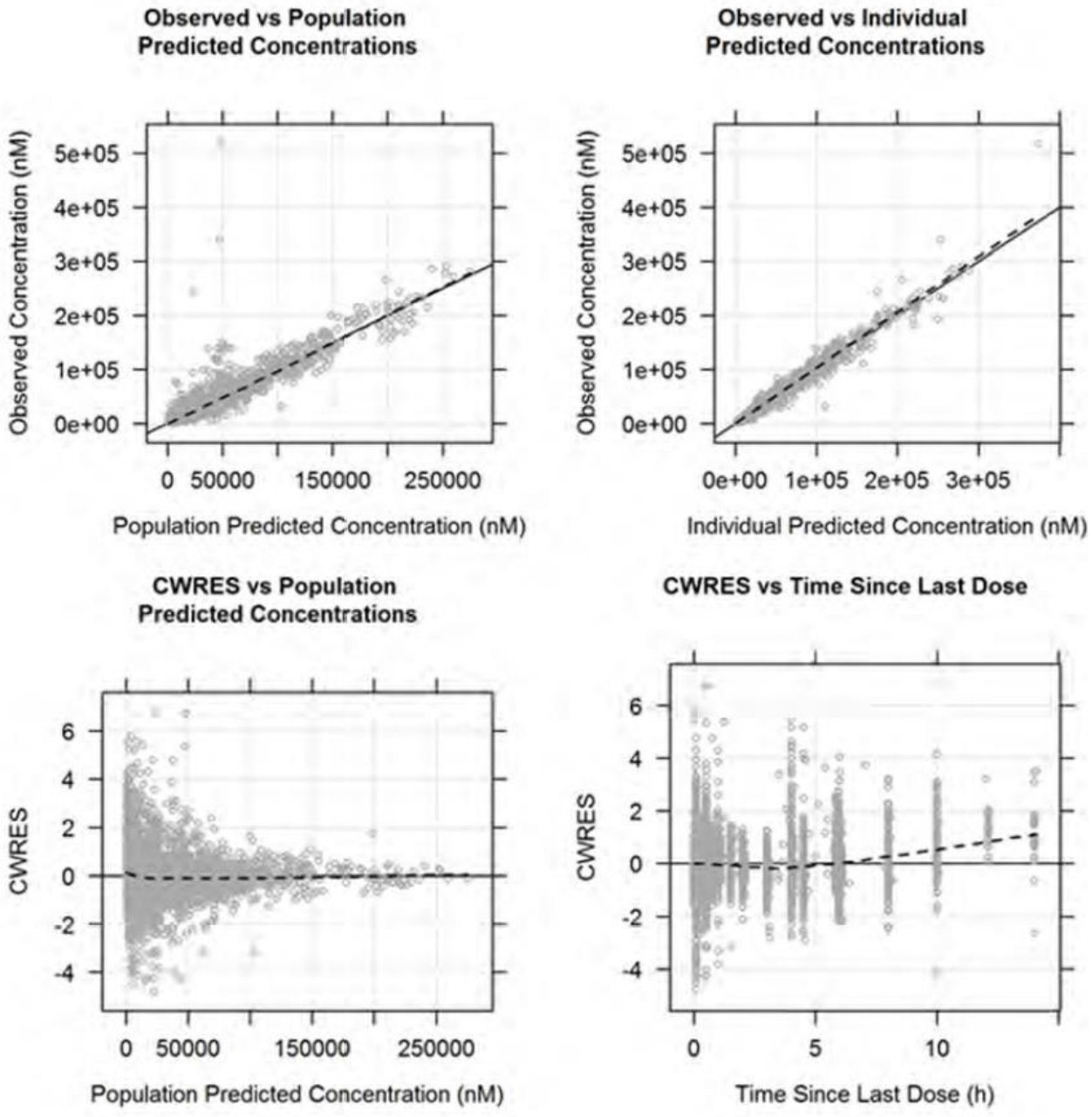
Source: Applicant's population pharmacokinetic analysis report; page 60 of 320.

Figure 20. Goodness of fit plots for imipenem's final population PK model



Source: Applicant's population pharmacokinetic analysis report; page 64 of 320.

Figure 21. Goodness of fit plots for relebactam' s final population PK model



Source: Applicant's population pharmacokinetic analysis report; page 65 of 320.

Figure 22.Visual Predictive Check (Dose Normalized) Stratified by Health Status relebactam

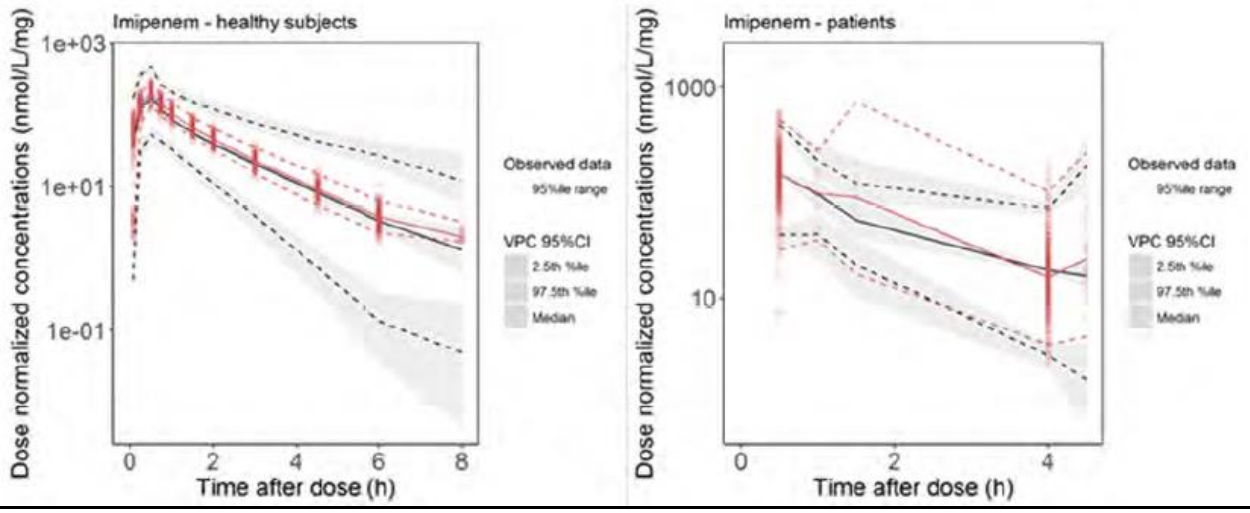
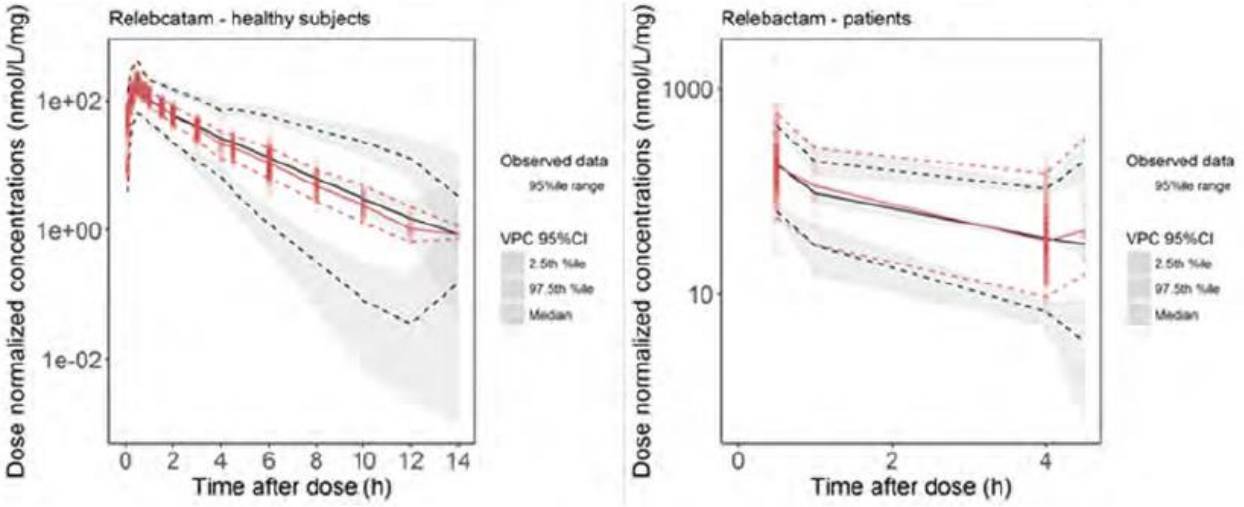


Figure 23. Visual Predictive Check (Dose Normalized) Stratified by Health Status for imipenem



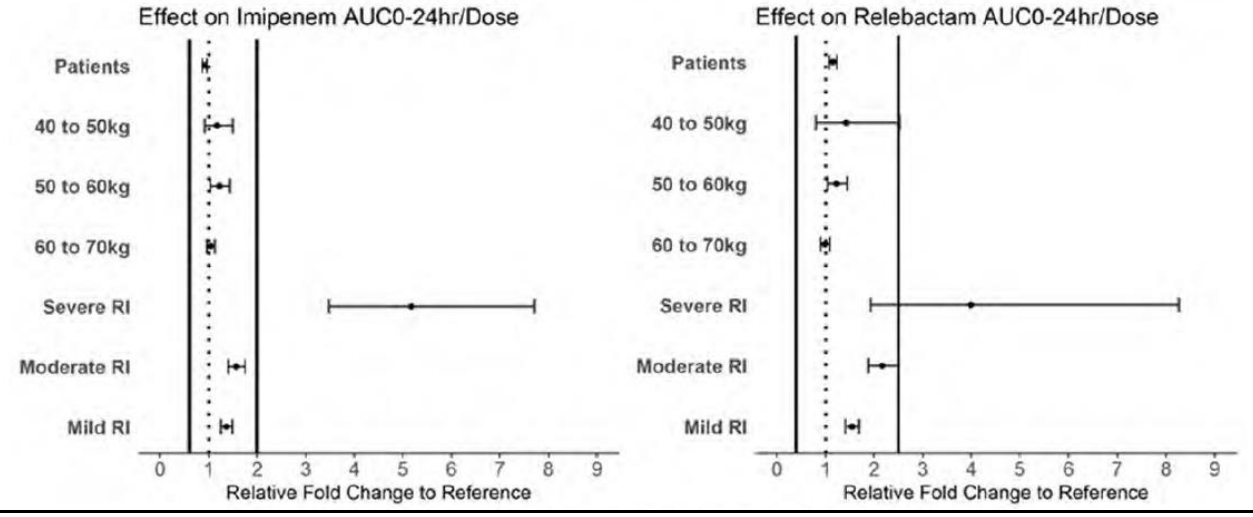
Source: Applicant's population pharmacokinetics report; Page 70 and 71 of 320

Covariate effects on steady state exposure

The applicant performed a post-hoc analysis to determine if the identified covariates have clinically meaningful influence on the steady state exposure of imipenem and relebactam. In the post-hoc analysis, steady state AUC0-24h were simulated (using post-hoc parameter estimates) and compared between the reference population on one hand and specific populations on another hand. Specific populations were defined by different body weight categories, and renal impairment status. The characteristics of the reference population were: 70 – 100 Kg body weight range; 90 – 150 ml/min creatinine clearance range; and uninfected

healthy status (healthy volunteers). Figure 24 is a forest plot showing the fold difference in AUC0-24 between different specific populations compared to the reference population. Subjects with mild, moderate, and severe renal impairment had 1.37-, 1.57-, and 5.17-fold higher imipenem AUC0-24h compared to subjects with normal renal function. Similarly, they had 1.54-, 2.17-, and 3.99-fold higher relebactam AUC0-24 compared to subjects with normal renal function.

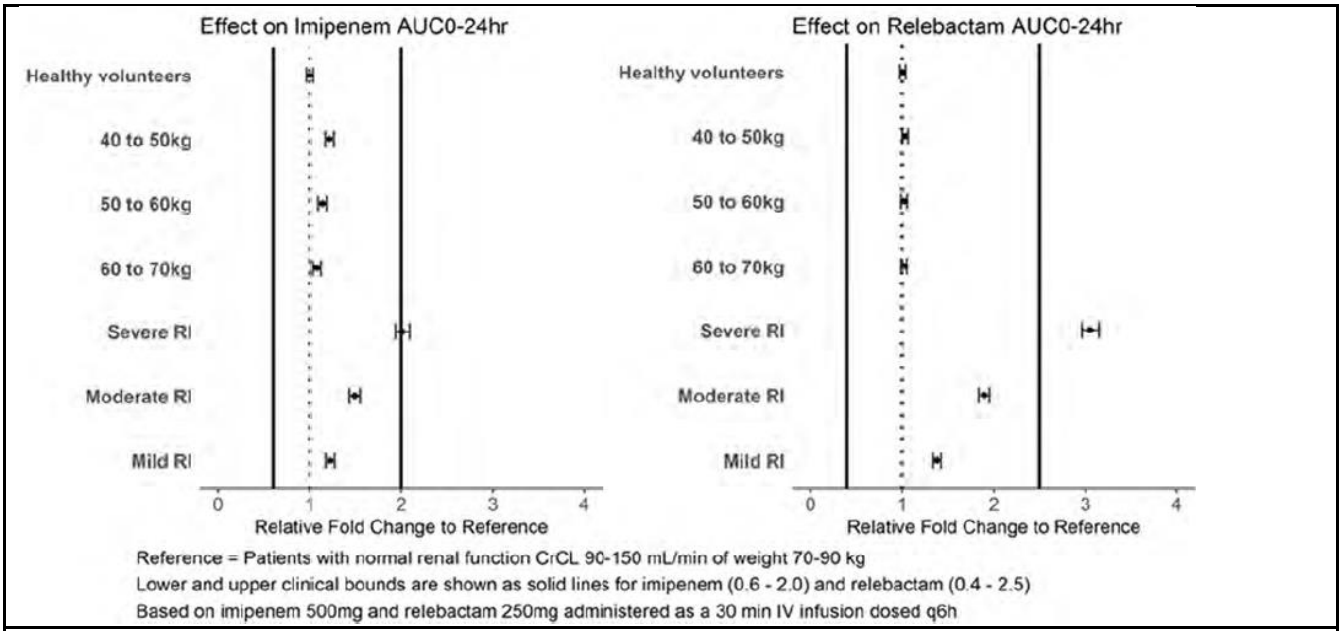
Figure 24. Impact of intrinsic factors on steady state dose-normalized AUC of imipenem and relebactam. Vertical solid lines represent lower and upper clinical bounds. Lower bound is threshold AUC0-24 ratio at which 90% of patients would exceed 6.5% Ft>MIC for imipenem and 5.2 fAUC0-24/MIC for relebactam. Upper bound is the 90th percentile of the simulated AUC0-24 for a dose of 1g Q6H for imipenem and 625 mg Q6H for relebactam. Error bars represent 90% confidence intervals of the mean fold change in AUC0-24h.



Source: Applicant's population pharmacokinetic report; page 68 of 320.

The applicant also performed assessment of covariate effects on steady state exposure using stochastic simulation of pharmacokinetic parameters. The reference population was patients with 70-100 Kg body weight range and 90-150 mL/min CRCL range. Covariance between weight and CRCL was considered. Results are as give in **Figure 25**.

Figure 25. Stochastic simulation of the Impact of Intrinsic Factors on Simulated Steady State AUC0-24hr of Imipenem and Relebactam



Source: Applicant's population pharmacokinetics report; Page 73 of 320

Pharmacokinetic parameters from simulations

The applicant used individual concentration-time profiles from stochastic simulations to summarize descriptive PK characteristics of imipenem and relebactam in patients with normal renal function (

Table **92**). From the simulations, the median steady-state average concentration of relebactam was determined to be 5.7 µg/mL or 4.4 µg/mL when corrected for protein binding (Unbound fraction for relebactam is 78%). Geometric mean total volume of distribution (V1 + V2) for imipenem and relebactam were 24.3 L and 19 L respectively.

Table 92. Population Pharmacokinetic Plasma Derived Geometric Mean (CV%) Parameters at Steady State in Simulated Patients with Normal Renal Function Dosed with Imipenem and Relebactam at 500mg and 250mg, respectively q6h as 30 Minute IV Infusions)

	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: Applicant's population pharmacokinetics report; Page 83 of 320

Exposure versus safety evaluation for relebactam

Regarding safety, relebactam 625 mg every 6 hours for 7 days was safe and well tolerated in healthy subjects with normal renal function. The safety of the recommended relebactam doses

among patients with renal impairment was evaluated through simulations. The safety criteria were the 90th percentile of AUC and Cmax for relebactam dose of 625 mg every 6 hours in subjects with normal renal function.
Table **93** shows the simulation results; greater than 95% of subjects remain below the upper limit for safety at the recommended relebactam doses.

Table 93. Percentage of subjects remaining below the upper-limit of safety for relebactam and imipenem

Table 20 Percentage of Patients Remaining Below the Upper Limit of Exposure (AUC0-24hr and Cmax) for Imipenem and Relebactam at Steady State

	Imipenem		Relebactam	
	AUC0-24hr	Cmax	AUC0-24hr	Cmax
End Stage Renal Disease (CrCL = < 15mL/min)	98.4	100	96.6	100
Severe Renal Impairment (CrCL = 15 – 30 mL/min)	99.8	100	99.8	100
Moderate Renal Impairment (CrCL = 30 – 60 mL/min)	99.7	100	100	100
Mild Renal Impairment (CrCL = 60 – 90 mL/min)	99.5	99.9	100	100
Normal Renal Function (CrCL = 90 – 150 mL/min)	99.6	99.7	100	100
Augmented Renal Function (CrCL = 150 - 180 mL/min)	99.8	100	100	100
Augmented Renal Function (CrCL = 180 - 210 mL/min)	100	100	100	100
Augmented Renal Function (CrCL = 210 - 250 mL/min)	100	100	100	100
Imipenem AUC0-24hr: 1959.5 μM.h; Cmax = 364.1 μM			Relebactam AUC0-24hr: 1655.2 μM.h; Cmax = 250.8 μM	

Source: Merck-7655A/Analysis/f-simulations/upper-limit-of-exposure-and-pta/percentage-below-upper-limit-simulated.R

Source: Applicant's population pharmacokinetics report; Page 79 of 320

1.1.4. Reviewers comments

The applicant followed acceptable pharmaco-statistical principles for pharmacokinetic model development. However, due to collinearity between body-weight and creatinine clearance, the correct effect of renal function on drug-clearances could be obtained by fixing body-weight coefficients to 0.75 and 1 for clearance (CL and Q) and volume (V1 and V2) parameters respectively. Reviewer applied this alternative modeling strategy. A linear model of CRCL versus WT was fitted and used to obtain CRCL value for a typical 70kg person. Individual clearance values for a 70Kg person was calculated using Equation 1 below.
Equation 1. Individual drug clearance dependence on creatinine clearance and body-weight

$$CL_i = TV_{CL(70Kg)} \times \left(\frac{CRCL_i}{106}\right)^{\theta_{CRCL}} \times \left(\frac{WT_i}{70}\right)^{0.75}$$

The parameter estimates from the reviewer's alternative model are given in the table below.

Imipenem			*Relebactam*	
Parameters	*Estimates (RSE%)*	*95% Confidence interval*	*Estimates (RSE%)*	*95% Confidence interval*
CL(L/hr/70Kg)	*11.6 (2)*	*11.1 – 12.0*	*6.84 (2)*	*6.5 – 7.5*
V1(L/70Kg)	*14.6 (3.4)*	*13.6 – 15.5*	*10.3 (2.9)*	*9.7 – 10.8*
V2(L/70Kg)	*5.47 (3.6)*	*5.1 – 5.8*	*6.1 (3.4)*	*5.6 – 6.4*
Q(L/70Kg)	*10.4 (6.2)*	*9.1 – 11.7*	*9.7 (6.7)*	*8.4 – 10.9*
Covariates on CL				
CRCL (Power)	*0.453 (8.4)*	*0.389 – 0.527*	*0.753 (8.6)*	*0.626 – 0.88*
WT (Power)	*0.75 FIXED*	*-*	*0.75 FIXED*	*-*
Covariates on V1				
WT (Power)	*1 FIXED*	*-*	*1 FIXED*	*-*
HLTH	*-0.292 (9.3)*	*-0.346 - -0.238*	*-*	*-*
Random effects				
	CV% (Shrinkage)	*RSE%*	*CV% (Shrinkage)*	*RSE%*
BSV on CL	*52 (5)*	*9.3*	*45 (16.4)*	*11.7*
BSV on V1	*75 (7.3)*	*11.7*	*60 (19.7)*	*11.6*
BSV on V2	*33 (53.5)*	*45.2*	*35 (51.2)*	*39.4*
Corr CL~V1	*0.562*	*12*	*0.362*	*12*
Residual errors				
Proportion error	*0.16 (19)*	*6.7*	*15 (14)*	*5.7*

The parameter estimates for a 70Kg person estimated from the reviewers' alternative model are comparable to parameter estimates for a 76Kg person estimated from the applicant's final model. However, reviewers' model estimates lower correlation between clearance and volume compared to the correlations estimated by the applicant's model.
Due to comparable parameter estimates between the reviewer and the applicant's models, the reviewer concludes that the applicant's final population pharmacokinetic models for both imipenem and relebactam adequately described the observed concentrations in healthy and patient populations. Simulations from the applicant's model provides useful information on steady state pharmacokinetic parameters in patients. Furthermore, the simulations show the influence of renal impairment on relebactam and imipenem exposure and therefore support the applicant's label recommendation.

1.2. Population PKPD analyses

1.2.1. Introduction

The applicant performed several experiments to evaluate the utility of relebactam at restoring the anti-bacterial activity of imipenem against resistant strains of pseudomonas aeruginosa and carbapenemase producing Enterobacteriaceae. The experiments included in-vitro checkerboard and hollow-fiber (HF) susceptibility studies and in-vivo murine infection model studies. The data generated from each experiment were analyzed individually to generate insight on the restorative activity of relebactam. The parameters generated from individual studies were integrated in a translational PKPD model and subsequently used to predict probability of cure after 7 days imipenem/relebactam treatment.

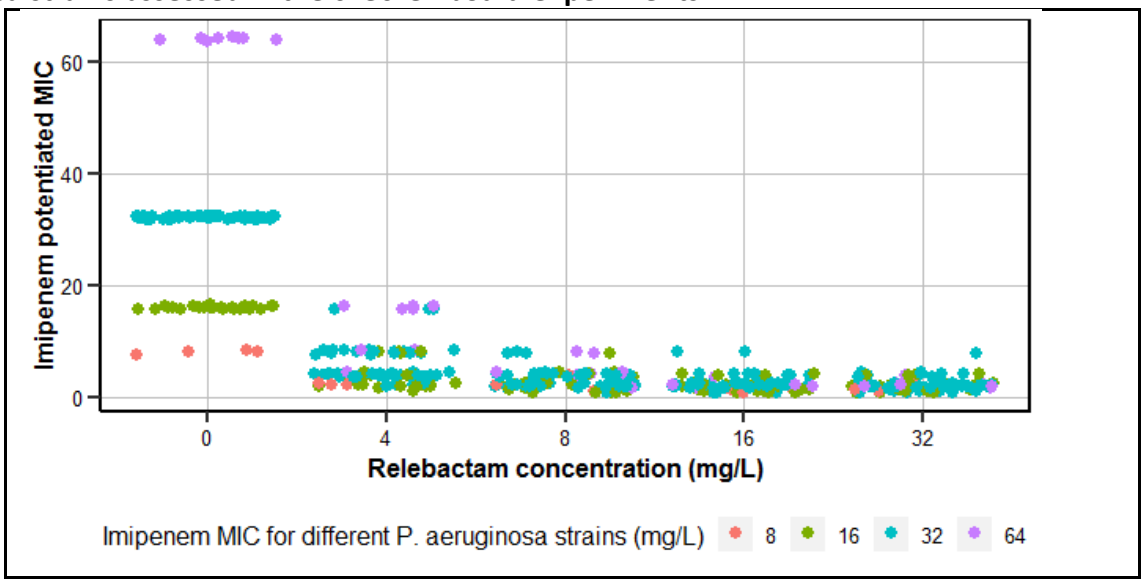
The objective of this review is to assess the raw-results, assumptions and parameters derived from the different experiments and to perform alternative PKPD analyses and simulations based on justifiable conservative assumptions.

1.2.2. Methods and Results

1.2.2.1. Modelling in-vitro relebactam concentration-vs-potentiated imipenem MIC Data

The applicant used checker-board assays to generate data on relebactam potentiation of imipenem in-vitro antibacterial activity against non-susceptible strains of P. Aeruginosa and Enterobacteriaceae. The non-susceptible strains of *P. Aeruginosa* included 107 clinical isolates contained in Merck's multi-drug resistant predictor panel which is an expanded panel of resistant strains collected from USA, south America and Europe. The non-susceptible strains of Enterobacteriaceae included clinical isolates of bacteria expressing Class A and C beta-lactamases. For each isolate, data was obtained on imipenem MIC when incubated alone (Un-potentiated MIC) or with different concentrations of relebactam (Potentiated MICs). The experiments were replicated three times. Figure 26 is a scatter plot of potentiated MIC versus relebactam concentration from the checker-board experiments.

Figure 26. Imipenem potentiated MIC versus relebactam concentrations for different P. aeruginosa strains assessed in the checker-board experiments



Source: reviewer's independent data exploration.

Modeling

The applicant developed a stochastic inhibitory Imax model to describe the relationship between relebactam concentration and potentiated MICs. The stochastic part of the model accounted for inter-strain differences in relebactam potentiation of imipenem (decrease MIC). *Equation 2* shows the inhibitory Imax model used to fit the data.

Equation 2. Inhibitory Imax model of relationship between relebactam concentration and potentiated imipenem MIC

$$MIC_p = MIC_0 \times \left(1 - \frac{I_{max} \times REL}{IC_{50} + REL}\right)$$

Where: MIC_0 is imipenem MIC without relebactam; MIC_p is relebactam potentiated MIC; I_{max} is maximum fractional decrease of MIC, IC_{50} is relebactam concentration at which half I_{max} is achieved, REL is relebactam concentration; PROP is proportional residual error.

Results

The parameter estimates of the model are given in
Table **94** .

Table 94. Parameter estimates of the inhibitory Imax model of relebactam versus potentiated MIC

Parameters	Description	Estimates (RSE)	Variance (RSE)	Variability (CV%)
I_{max}	Maximum fractional decrease of MIC	0.944 (0.7%)	0.0013 (52%)	-
IC_{50}	Concentration at which half I_{max} is achieved	0.533 (10%)	0.738 (22.1%)	-
PROP	Proportional residual error	0.0475 (10.2%)	-	-

Reviewer's comments

This analysis was relevant as it enabled prediction of potentiated imipenem-MICs for different P. aeruginosa strains in a translational PKPD model. The applicant's model to describe potentiated MIC versus relebactam concentrations is acceptable. The reviewer was able to reproduce the model parameter estimates as reported by the applicant.

1.2.2.2. Determination of relebactam PKPD indices and targets using murine-thigh infection model

Data

The applicant used murine thigh infection models to generate data on relebactam potentiation of imipenem bactericidal and bacteriostatic activities in-vivo. Four non-susceptible strains of P. aeruginosa (CLB24266, CLB24227, CLB24228, CLB24354) and two non-susceptible strains of K. pneumoniae (6755, 6339) were used for the experiments. Female CD1 mice were rendered neutropenic by treatment with cyclophosphamide starting from 4 days before inoculation with 5×10^6 colon forming units (CFU) of the resistant strains. Treatment was subsequently initiated

two hours after infections. One group of mice was treated with different doses of imipenem/cilastatin alone to establish dose-response relationship of imipenem. Another group was treated with imipenem/cilastatin/relebactam combinations. The imipenem/cilastatic/relebactam treatment group was further subdivided into different imipenem-dose sub-groups to receive different doses of imipenem. For each imipenem-dose sub-group the mice were further subdivided into sub-group to receive different doses of relebactam; and hence allow for the development of exposure-response relationship for relebactam in presence of fixed imipenem exposure. Pharmacokinetic information was collected to enable determination of exposure metrics for both imipenem and relebactam. The exposure metrics for both imipenem and relebactam included area under the concentration-time curve (AUC0-24), maximum observed concentration (Cmax), fraction of time above critical concentration (%*f*T>C), and total daily dose (TDD). The applicant did not evaluate Cmax/MIC, and fraction of time above MIC (%*f*T>MIC) as potential PKPD indices. Pharmacodynamic information was counts of colony forming units (CFU) 2 hours after infection (Baseline, at initiation of treatment) and 24 hours after treatment. Drug effect was determined as the 24-hour change from baseline in log10(CFU) (Difference between 24- and 2-hour log10 transformed CFU (dlogCFU)).

Modeling

The applicant applied a deterministic Hill model for each strain to describe the observed relationships between different exposure metrics and the drug effect. Ordinary least square regression method was used to fit the models to the observed data. A model with best fit was determined through comparison of respective regression coefficients (R^2)

Determination of PKPD index and target

The exposure-metric whose Hill model had the largest R^2 was chosen as the appropriate PKPD index. The applicant determined PKPD target for stasis, and this was the value of the PKPD index at which there was no observable bacteria growth or killing.

Results

Table 95 shows the calculated relebactam PKPD targets for different strains of *P. aureginosa* and at different background doses of imipenem. For *P. aeruginosa strain CLB 24226*, the table indicates lower PKPD target for higher background dose of imipenem. Imipenem dose of 15.9 mg/Kg in mice was considered equivalent to human dose of 500 mg Q6H. Only one strain of *P. aeruginosa* (CLB 24228) was tested at the human equivalent dose; the PKPD target for this strain was the AUC of 27.2 mg.hr/L. The applicant calculated AUC/MIC target by simply dividing the AUC by strain specific MIC.

The applicant assumed that the targets for other strains than CLB 24228 could be lower at human equivalent doses of imipenem; and therefore, the average of the observed PKPD targets was selected as a conservative PKPD target for relebactam (i.e 5.2 *fAUC*0-24/MIC).

Table 96 shows the relebactam PKPD targets for resistant strains of both *P. aureginosa and K.pneumoniae.* The table shows a PKPD target of 25.2 *fAUC*0-24/MIC for *K. pneumoniae 6339*. **Table 96** also shows potentiated MICs obtained from checker-board experiments conducted by Merck (column 3) compared to those reported by Mavridou *et al,.*(1) *(*column4*)*. The values from experiments conducted by Merck are on average 8 times higher than those reported by Mavridou *et al*. Merck did not determine potentiated MIC for *K. pneumoniae 6755*.

The applicant performed another analysis to evaluate AUC/MIC targets. In this analysis data were pooled from experiments where imipenem dose levels were 8 mg/Kg and 15.9 mg/Kg. Results from this analysis are given in Table 97

Table 95. Relebactam PKPD target in mouse thigh model of infection at different imipenem background doses

Strain	Imipenem/REL MIC[†‡] (mg/L)	Imipenem Dose (mg/kg) (fold of humanized dose)	Free AUC for Stasis (mg.hr/L)	*f*AUC/MIC
P. aeruginosa CLB 24226	4	2 (0.125X)	32.8	8.2
P. aeruginosa CLB 24226	4	4 (0.25X)	42.2	10.6
P. aeruginosa CLB 24226	4	8 (0.5X)	12.5	3.1
P. aeruginosa CLB 24354	16	8 (0.5X)	45.2	2.8
P. aeruginosa CLB 24227	2	8 (0.5X)	6.4	3.2
P. aeruginosa CLB 24228	8	15.9 (1X)	27.2	3.4
		Mean *f*AUC/MIC		5.2

[†]Imipenem MIC in presence of 4 mg/L of REL [Ref. 4.2.1.1: PD001MK7655]

Source: Applicant's Translational PKPD Analysis report; page 31 of 159.

Table 96. Relebactam PKPD targets for thigh infection model for both P. aeruginosa and K.pneumoniae strains

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; NA = not available; NC = not calculated; REL = Relebactam; µM = micromolar;

Source: PD017 [Sec. 2.6.3.1]; Mavridou et al, 2015 [Ref. 4.3: 04M693]; Merck Modeling and Simulation Report, 2018 [Ref. 5.3.5.3: 04WBXC].

Source: Applicant's non-clinical overview; page 28 of 53

Table 97. Relebactam PK target from in vivo neutropenic mouse thigh model

Species	Strains	Growth Control vs IMI-Alone	IMI Dose(mg/kg) at Q2H	Derived *f*AUC/MIC Target	
				Stasis	1-log kill
P. aeruginosa	24226, 24227, 24228, 24354	Growth Controls	8,15.9	3.3	4.3
	24226, 24228, 24354	Growth Controls	8,15.9	3.3	4.3
	24226, 24228, 24354	Growth Controls+IMI-alone	8,15.9	3.3	4.3

Source: Efficacy information amendment – Response to FDA; page 2 of 5

Reviewer's comments

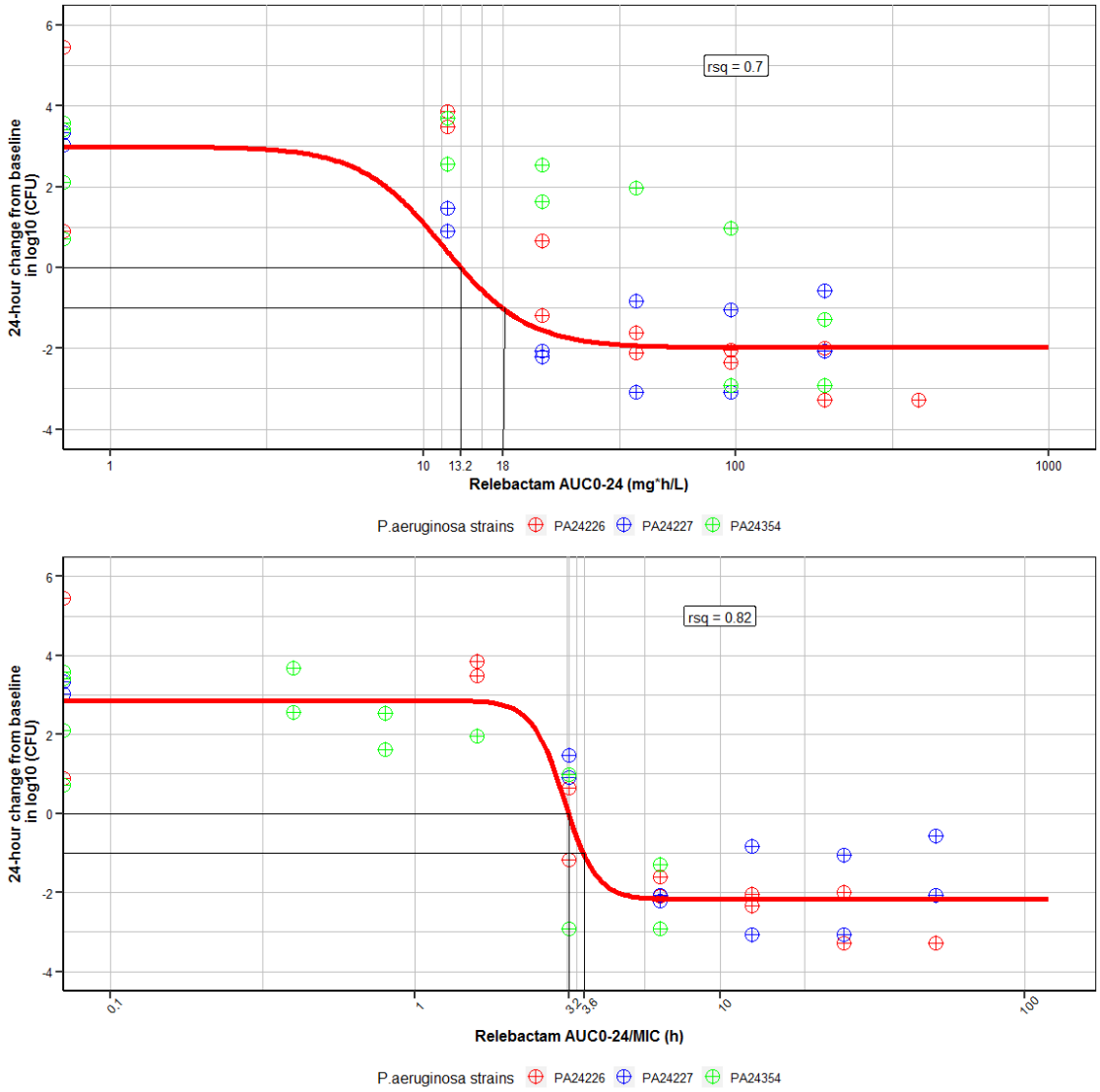
In the initial submission, the applicant did not assess AUC/MIC as a potential PKPD index. Nevertheless, the applicant used AUC/MIC as the relebactam PKPD index for efficacy. The applicant determined AUC/MIC targets for stasis by dividing AUC0-24 targets for stasis with potentiated MICs for different strains. After the reviewers' information request to the applicant, the applicant evaluated AUC/MIC targets for stasis and 1-log kill targets. However, it was not clear as to which was a better PKPD index between AUC and AUC/pMIC. Furthermore, the relebactam PKPD target that is based on a wide range of imipenem exposures remained unknown. The reviewer fitted the inhibitory Imax model to the observed data to determine a better PKPD index between AUC0-24 and AUC0-24/MIC. The analyses in the following sub-

section assesses inhibitory model-fits between AUC0-24 and dlog10CFU and between AUC0-24/MIC and dlog10CFU.

Comparison of model fit between AUC0-24 vs dlog10CFU and between AUC0-24/MIC vs dlog10CFU

Three pseudomonas strains (PA24226, PA24227, PA24354) with different relebactam potentiated MIC were used for this assessment. The potentiated MICs for the three strains are 4, 2, and 16 µg/mL for PA24226, PA24227 and PA24354 respectively. In the murine thigh infection model experiments, relebactam was administered at different total daily doses ranging from 0-384 mg/Kg. In the experiments considered for this assessment, imipenem was administered at a dose of 8 mg/Kg for all the 3 strains. Data from separate strain specific experiments were pooled. AUC0-24 and AUC0-24/pMIC were calculated. **Figure 27** *below shows sigmoid inhibitory Imax model fit for AUC0-24 vs dlog10CFU and AUC0-24/MIC vs dlog10CFU. PKPD target for stasis and 1 log-kill are also indicated in the figure. The results show that AUC/pMIC is a better PKPD index compared to AUC.*

Figure 27. AUC0-24 and AUC0-24/MIC versus 24-hour from baseline in log10 CFU. AUC/MIC is a better PKPD index compared to AUC0-24



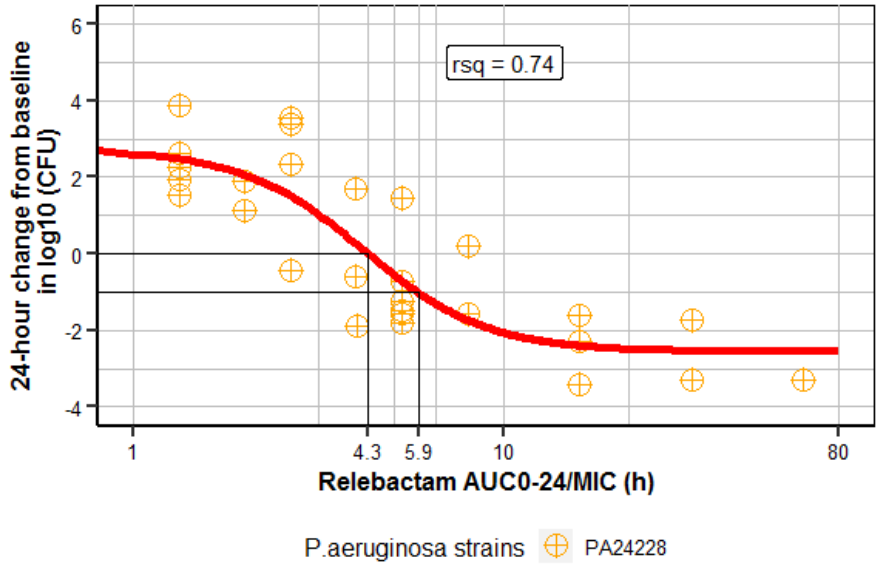
AUC/MIC targets determined by individual Murine thigh model experiments.

For each reported murine thigh model experiment, AUC and AUC/MIC were calculated and used to determine AUC/MIC target for individual strains at different imipenem doses. The sub-sections below explore model-fit for the inhibitory sigmoid-model to datasets from Murine thigh model experiments for different P. aeruginosa strains at different imipenem doses.

AUC/MIC targets for PA24228 at imipenem dose of 15.9 mg/Kg

PA24228 has imipenem MIC of 32 mg/L and potentiated imipenem MIC of 8 mg/L. **Figure 28** *shows stasis and 1-log kill targets of 4.3 and 5.9 respectively. These targets are higher than those observed at a lower imipenem dose of 8 mg/Kg when data from three strains (PA24226, PA24227, PA24354) are pooled (See section 2 above).*

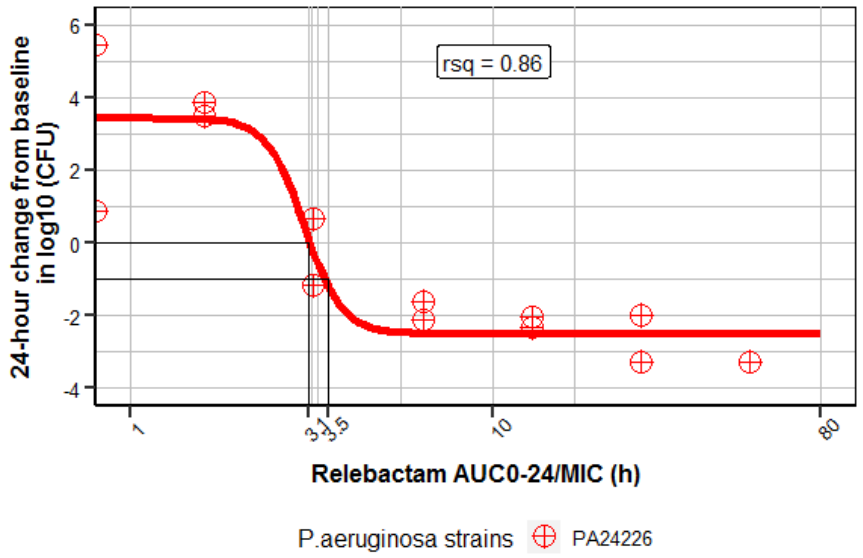
Figure 28. AUC0-24/MIC versus 24-hour change from baseline in log10 CFU for PA24228 at imipenem TDD of 15.9 mg/Kg



AUC/MIC targets for PA24226 at imipenem dose of 8 mg/Kg

PA24226 has imipenem MIC of 8 mg/L and potentiated imipenem MIC of 4 mg/L. **Figure 29** *shows stasis and 1-log kill targets of 3.1 and 3.5 respectively.*

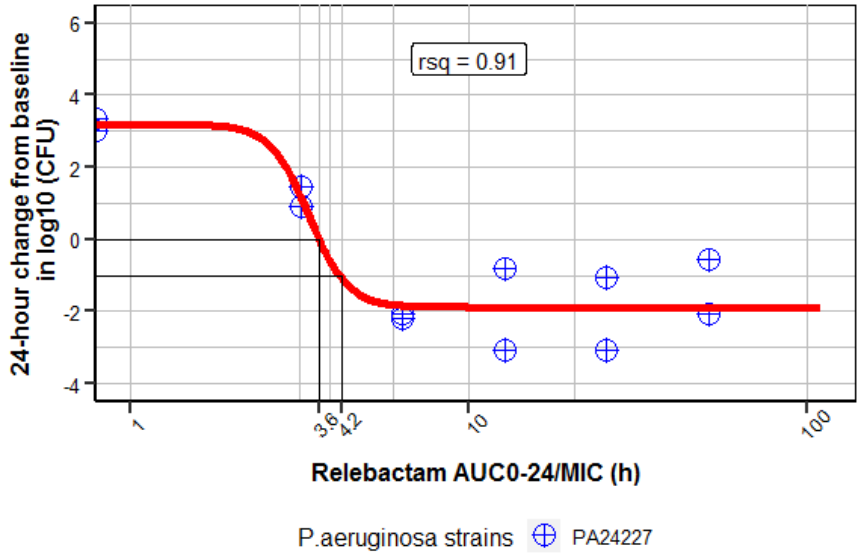
Figure 29. AUC0-24/MIC versus 24-hour change from baseline in log10 CFU for PA24228 at imipenem TDD of 8 mg/Kg.



AUC/MIC targets for PA24227 at imipenem dose of 8 mg/Kg

PA24227 has imipenem MIC of 4 mg/L and potentiated imipenem MIC of 2 mg/L. **Figure 30** *shows stasis and 1-log kill targets of 3.6 and 4.2 respectively.*

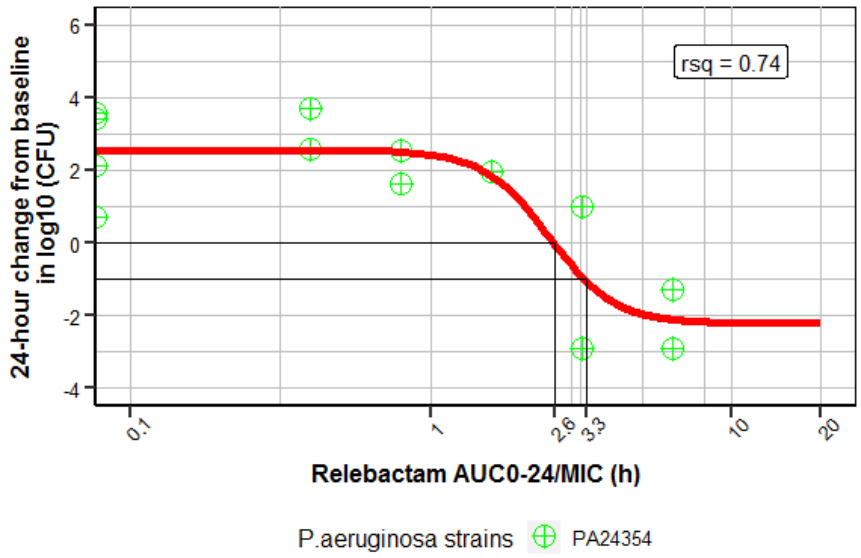
Figure 30. AUC0-24/MIC versus 24-hour change from baseline in log10 CFU for PA24227 at imipenem TDD of 8 mg/Kg



AUC/MIC targets for PA24354 at imipenem dose of 8 mg/Kg

PA24354 has imipenem MIC of 32 mg/L and potentiated imipenem MIC of 16 mg/L. **Figure 31** *shows stasis and 1-log kill targets of 2.6 and 3.3 respectively.*

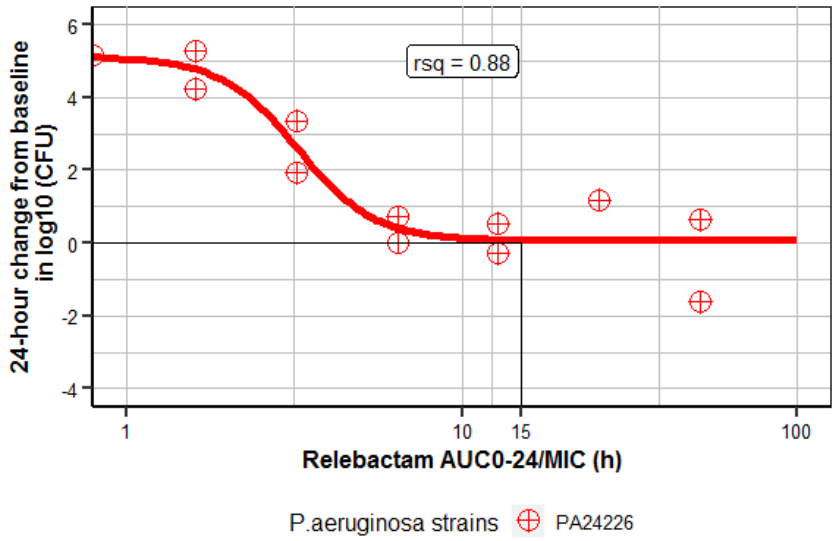
Figure 31. AUC0-24/MIC versus 24-hour change from baseline in log10 CFU for PA24354 at imipenem TDD of 8 mg/Kg



AUC/MIC targets for PA24226 at imipenem dose of 4 mg/Kg

PA24226 has imipenem MIC of 8 and potentiated MIC of 4. **Figure 32** *shows stasis targets of 15, but 1-log kill target is not achieved at the imipenem dose of 4 mg/Kg.*

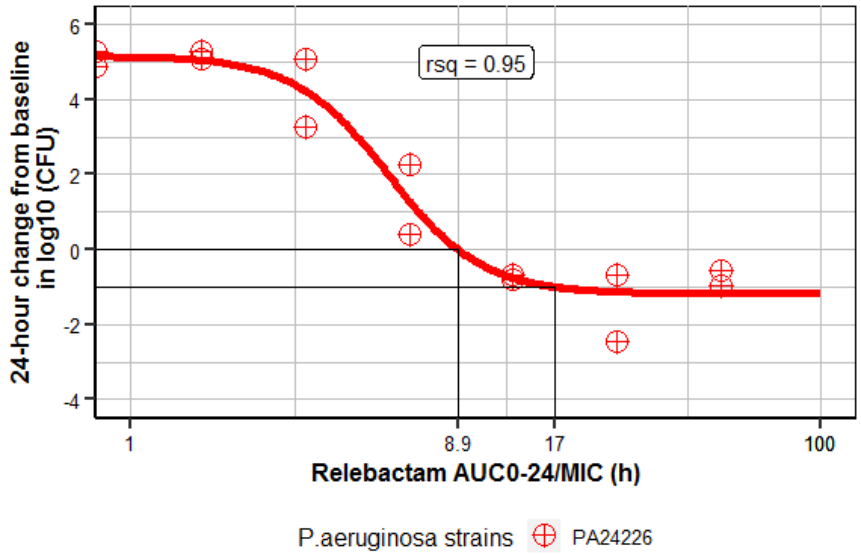
Figure 32. AUC/MIC vs 24-hour change from baseline of log10 (CFU) for PA24226 at imipenem TDD of 4 mg/Kg



AUC/MIC targets for PA24226 at imipenem dose of 2 mg/Kg

Figure 33 *shows stasis and 1-log kill targets of 8.9 and 17 respectively. These results show that 1-log kill is achieved at imipenem dose of 2 mg/Kg.*

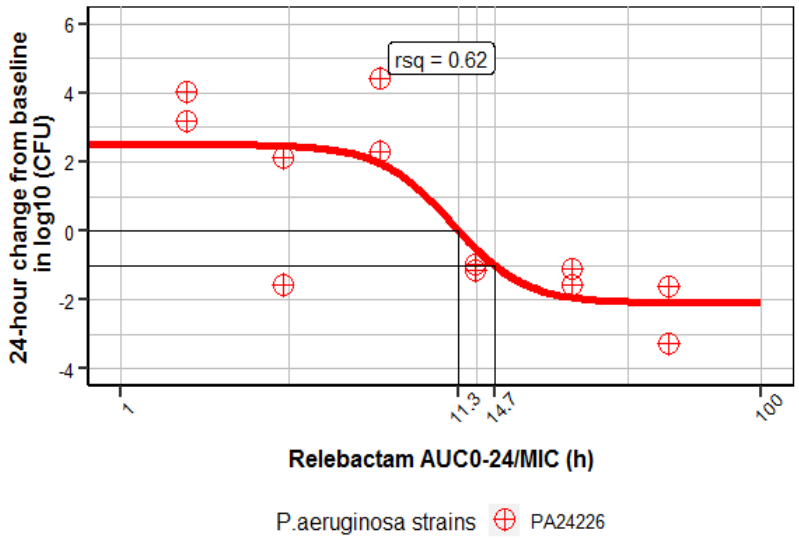
Figure 33.AUC/MIC vs 24-hour change from baseline of log10 (CFU) for PA24226 at imipenem TDD of 2 mg/Kg



AUC/MIC targets for PA24226 at imipenem dose of 1 mg/Kg

Figure 34 *shows stasis and 1-log kill targets of 11.3 and 14.7 respectively. These results show that 1-log kill is achieved at imipenem dose of 1 mg/Kg.*

Figure 34. AUC/MIC vs 24-hour change from baseline of log10 (CFU) for PA24226 at imipenem TDD of 1 mg/Kg

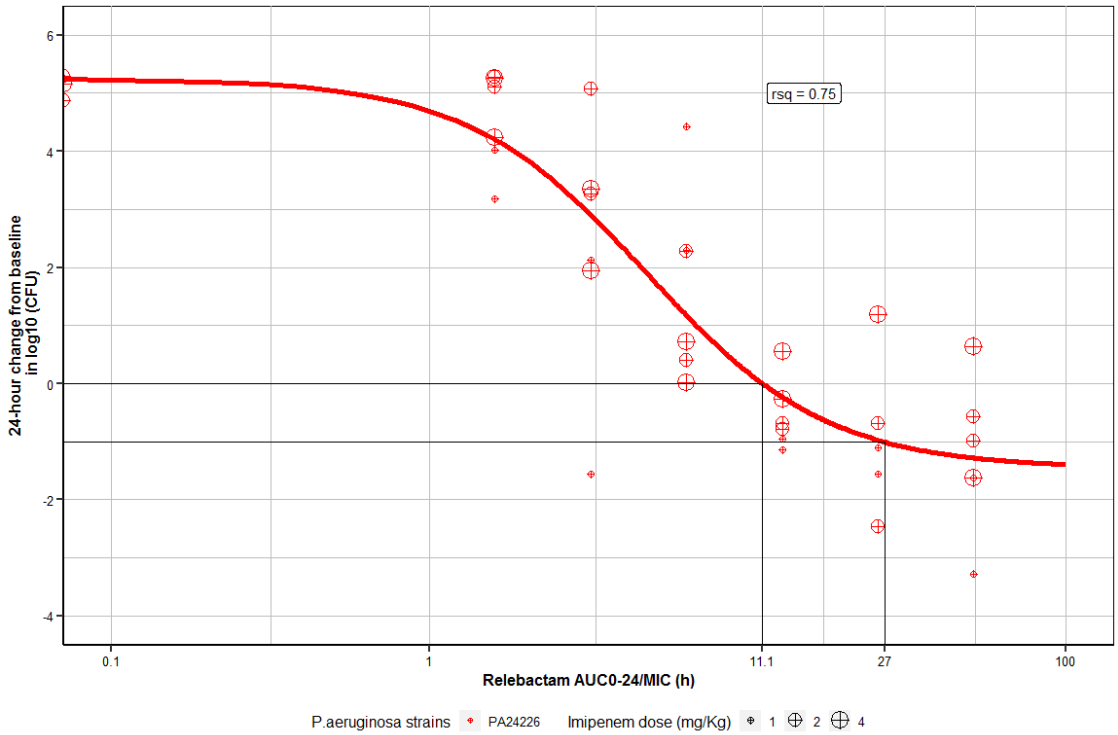


Analyzing data for pooled experiments for PA24226 regardless of imipenem dose

Data from experiments at imipenem doses of 1, 2, and 4 mg were pooled to determine relebactam PKPD targets at low imipenem exposures. The pooled analysis is justified by the fact that PKPD targets for imipenem doses of 1 and 2 mg/Kg were comparable. Furthermore,

imipenem doses of 1 and 2 mg/Kg indicated even higher activity (See sections above) compared to imipenem dose of 4 mg/kg.
The analysis of pooled data aimed provide a balanced information regarding imipenem/relebactam 1-log kill at low imipenem exposure and hence relebactam 1-log kill target at low imipenem exposures. Figure 35 shows stasis and 1-log kill targets of 11.3 and 27 respectively at low imipenem exposures.

Figure 35. AUC/MIC vs 24-hour change from baseline of log10 (CFU) for PA24226 at low imipenem exposure (pooled data for imipenem TDD of 1, 2, and 4 mg/Kg)



Analyzing Pooled data for all strains regardless of imipenem doses
Alternatively, data from all imipenem doses were pooled to determine relebactam PKPD targets at wide range of imipenem exposure (sub-therapeutic to therapeutic exposures). An inhibitory Imax model was fitted to the data to estimate mean values of the model parameters (Intercept, Imax, Index50, and sigmoidity factor). Further-more, non-parametric bootstrap was used to estimate lower and upper bound of the 95% confidence intervals (2.5th and 97.5th percentiles) of the model parameters. The lower and upper bounds of the 95% confidence intervals of the model parameters were used to predict upper and lower bounds of the 95% confidence intervals for stasis and 1-log kill targets.
Figure 36 *shows stasis and 1-log kill targets of 4.8 and 7.5 respectively at imipenem exposures ranging from 6.25% to 99% of human dose.*

Figure 36. AUC/MIC vs 24-hour change from baseline of log10 (CFU) for all strains and at imipenem exposure ranging from 6.25% to 99% of human dose

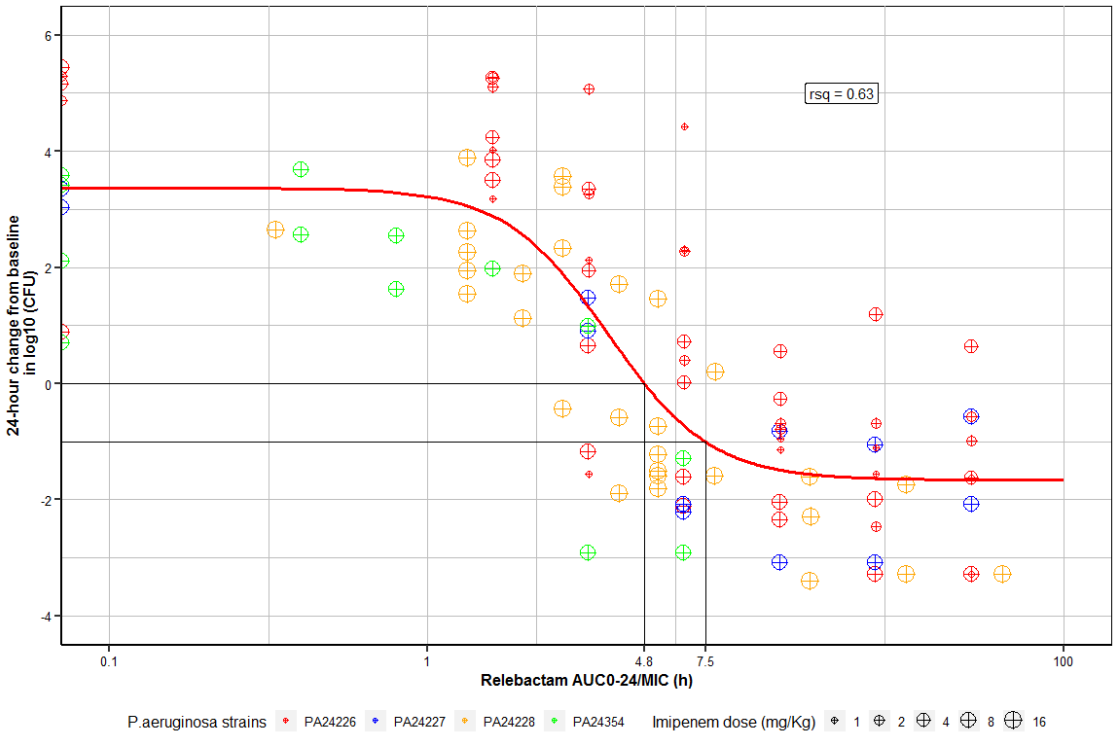
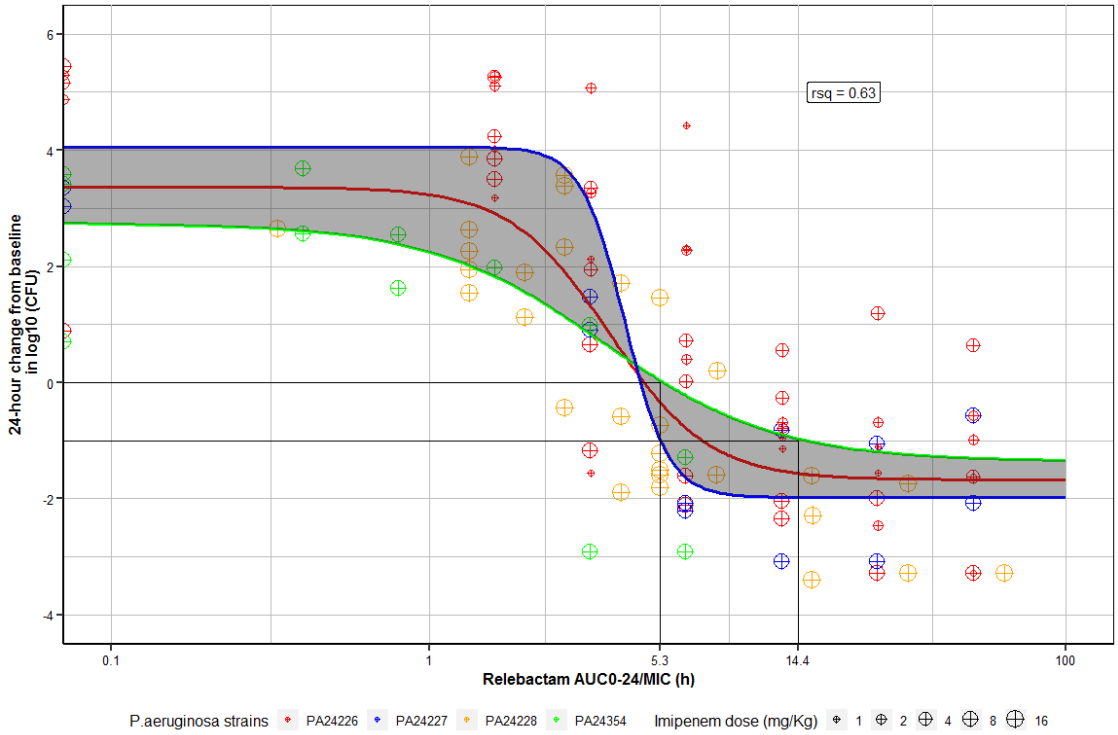


Figure 37 *shows stasis and 1-log kill targets of 5.3 and 14.4 respectively based on the lower bound of the 95% confidence interval on the model parameters.*

Figure 37. AUC/MIC vs 24-hour change from baseline of log10 (CFU) for all strains and at imipenem exposure ranging from 6.25% to 99% of human dose. Red line = median prediction; Blue and green lines are predictions from upper and lower bounds of 95% CI of model parameters respectively



Summary of AUC/MIC targets from different experiments

The **Table 98** *below shows a summary of AUC/MIC targets from the analyses in the above sections.*

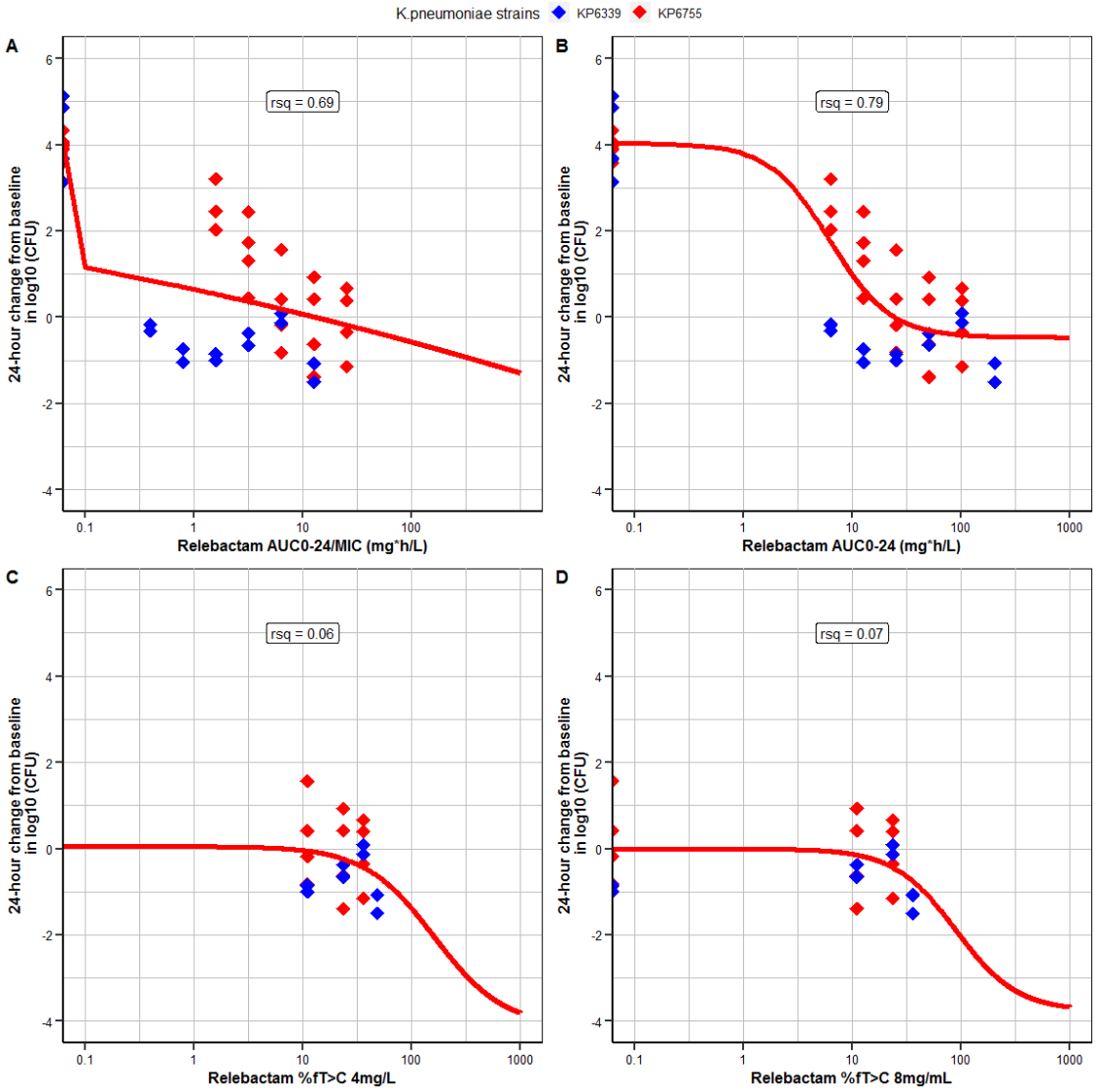
Table 98. AUC/MIC targets for different strains and at different Imipenem doses

P. Aeruginosa strains	*Number of experiments*	*MIC (mg/L)*	*Potentiated MIC (mg/L)*	*Imipenem Dose (mg/Kg)*	*Stasis Target (95%CI)*	*1-Log Kill target (95%CI)*
24226	*1*	*8*	*4*	*1*	*11.3*	*14.7*
24226	*1*	*8*	*4*	*2*	*8.9*	*17*
24226	*1*	*8*	*4*	*4*	*15*	*Inf*
24226	*3*	*8*	*4*	*1,2,4 (pooled)*	*11.1*	*27*
24228	*1*	*32*	*8*	*15.9*	*4.3*	*5.9*
24227, 24226, 24354	*3*	*4,8,32*	*2,4,16*	*8*	*3.2*	*3.6*
24227	*1*	*4*	*2*	*8*	*3.6*	*4.2*
24226	*1*	*8*	*4*	*8*	*3.1*	*3.5*
24354	*1*	*32*	*16*	*8*	*2.6*	*3.3*
24226, 24227, 24228,	*7*	*2, 4,8,32*	*2,4,8,16*	*1,2,4,8,16 (pooled)*	*4.8 (4.5 - 5.2)*	*7.5 (5.3 - 14.4)*

P. Aeruginosa strains	***Number of experiments***	***MIC (mg/L)***	***Potentiated MIC (mg/L)***	***Imipenem Dose (mg/Kg)***	***Stasis Target (95%CI)***	***1-Log Kill target (95%CI)***
24354						

Relebactam PKPD index and target for Klebsiella Pneumoniae
Relebactam *PKPD index* for *Klebsiella Pneumoniae* was investigated using two strains of *k. pneumoniae* exposed to imipenem doses that were half (8 mg/Kg) of the human equivalent dose (16 mg/Kg). These data were chosen to enable assessment of AUC/pMIC as a PKPD index. Figure 38 shows the model fit for different relebactam PKPD indices for k. pneumoniae. The figure shows that AUC is a better PKPD index.

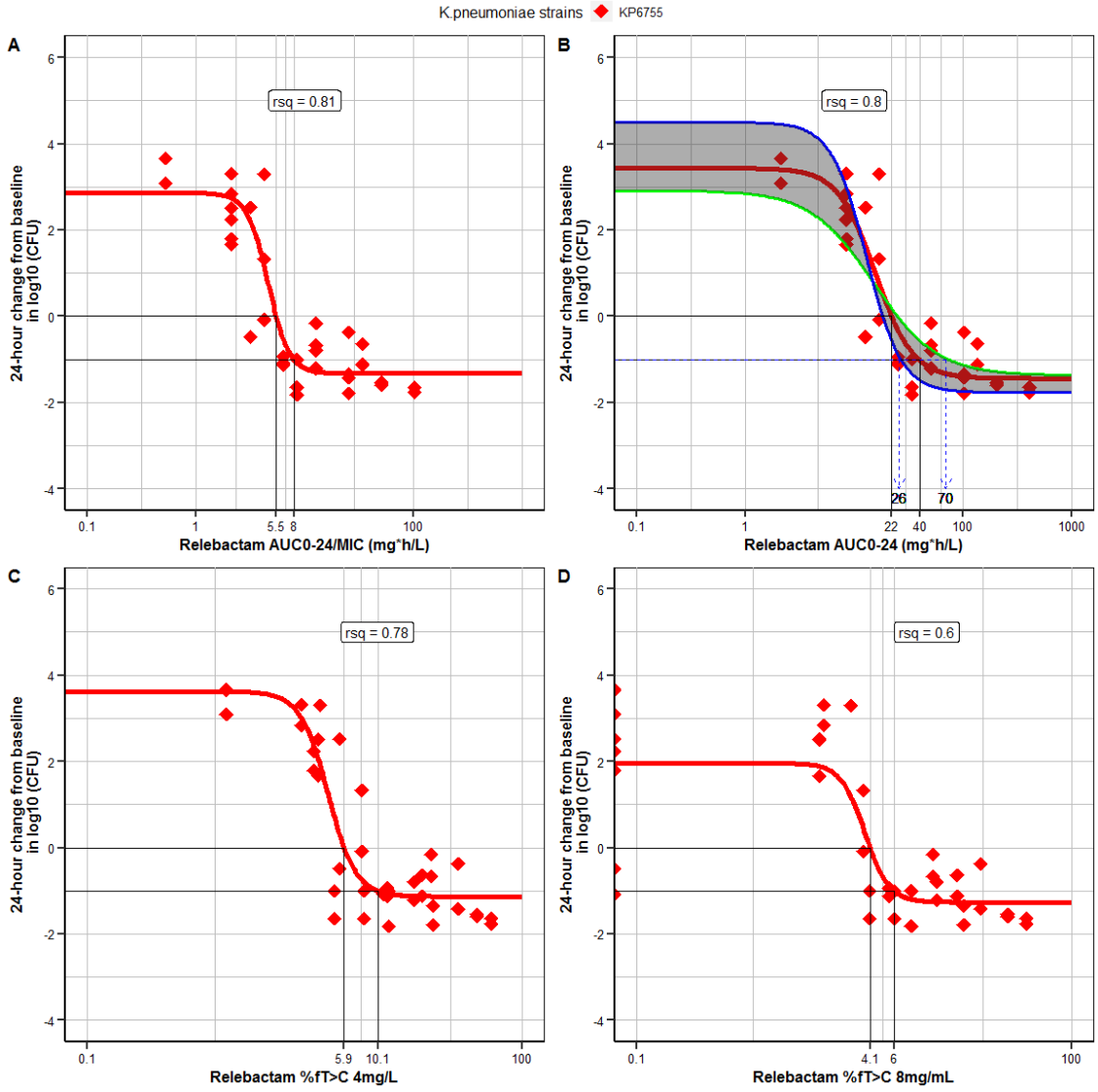
Figure 38. Model fit for different PKPD indices versus 24-hour from baseline in log10 CFU. AUC0-24 is better PKPD index compared to AUC0-24/MIC



Relebactam AUC0-24 targets for k. pneumoniae were investigated using data from an experiment that evaluated relebactam activity at imipenem exposure that were equivalent to human exposure. These data were chosen because experiments at lower imipenem exposures did not achieve 1-log kill at any of the tested relebactam doses. Only one k. pneumoniae strain (PK6755) was assessed at human equivalent exposure.

Figure 39 *shows model fit and PKPD targets for the different PKPD indices. The AUC targets for stasis (Panel B) and 1-log kill for KP6755 strain are 22 and 40 respectively. The 95% confidence interval for 1-log kill target was determined through non-parametric bootstrap analysis and ranged between 26 - 70 mg×h/L*

Figure 39. Model fit for different PKPD indices versus 24-hour from baseline in log10 CFU. AUC0-24 and AUC0-24/MICs are better PKPD index compared to AUC0-24



1.2.2.3. Modeling hollow-fiber relebactam exposure -vs-imipenem bactericidal activity

Data

The applicant also used in-vitro hollow-fiber (HF) experiments to evaluate relebactam potentiation of imipenem bacteriostatic and bactericidal activities. The hollow fiber system was designed such that it would emulate human two-compartment disposition kinetics of imipenem and relebactam with an elimination half-life (t1/2) of 1.5 hours for both drugs. The HF system simulated the free drug exposure in humans. The central compartment of the hollow-fiber was inoculated with approximately 10^5 CFU and incubated for 4 hours to allow the bacteria population to grow to 10^6 CFU/mL before treatment. The resistant strains used in the HF experiment were: Five strains of *P. Aeruginosa*, six strains of *K. Pneumoniae,* two strains of *E. Coli,* one strain of *S. marcescens,* and one strain of *K.oxytoca*. The un-potentiated and relebactam-potentiated imipenem MIC of the tested strains are given in Table 99. The HF

systems were treated with imipenem only or imipenem/relebactam combinations for up to 3 days. The treatment designs for the different HF experiments are given in Table 100. In some experiments, samples for quantification of viable bacteria counts were collected at 0, 3, 6, 12, 18, 24, 36, 42, 48, 54, 60, 66, and 70 hours for initiation of treatment. In other experiments, additional samples were collected at 72, 96, 120, 140, 144, 168, and 196 hours after initiation of treatment. The HF exposure metrics for both imipenem and relebactam were: AUC0-24, AUC0-24/MIC, Cmax, %*f*T>MIC, and %*f*T>Ct (Where the tested Ct were 1 µg/mL, 2 µg/mL, and 4 µg/mL).

Modeling

The applicant applied a deterministic inhibitory Imax model to the pooled data from all experiments/strains to describe the observed relationships between different exposure metrics and the drug effect. Drug effect was defined as change in log10(CFU) between 0 and 24 hours after drug treatment. The exposure-metric whose model fit had the largest R^2 was chosen as the appropriate PKPD index and its stasis target was the value at which there was no observable growth or killing.

Table 99. Imipenem-Resistant Strains Evaluated in the Hollow Fiber Infection model and included in the translational PKPD model development.

Organism	Isolate	Imipenem MIC (mg/L)	Imipenem/REL MIC (mg/L) †
P. aeruginosa	CLB 24226	32	4
P. aeruginosa	CLB 24227	8-16	2
P. aeruginosa	CLB 24228	32	8
P. aeruginosa	CLB 24354	64	16
P. aeruginosa	CL 5701	16	2
Klebsiella pneumoniae	CL 6339	64	1
Klebsiella pneumoniae	CL 6569	256	4
Klebsiella pneumoniae	CLB 26410	> 256	8
Klebsiella pneumoniae	CL 5763	32	0.5
Klebsiella pneumoniae	CL 6838	16	0.5
Escherichia coli	IHMA 1224137	8	≤ 0.5
Escherichia coli	IHMA 1231530	4	0.5
Klebsiella pneumoniae	IHMA 516426	16	0.5
Serratia marcescens	IHMA 1203541	8	1
Klebsiella oxytoca	IHMA 1211369	32	0.25
Klebsiella pneumoniae	IHMA 520284	16	0.25

Table 100. Design Summary of HF Studies

Experiment	P.Aeruginosa	Imipenem	Freq	REL	Freq
HF2012-007	CL5701	0	q6h	0	q6h
HF2011-005	CL5701	0	q6h	0	q6h
HF2012-007	CL5701	200	q6h	13	q6h

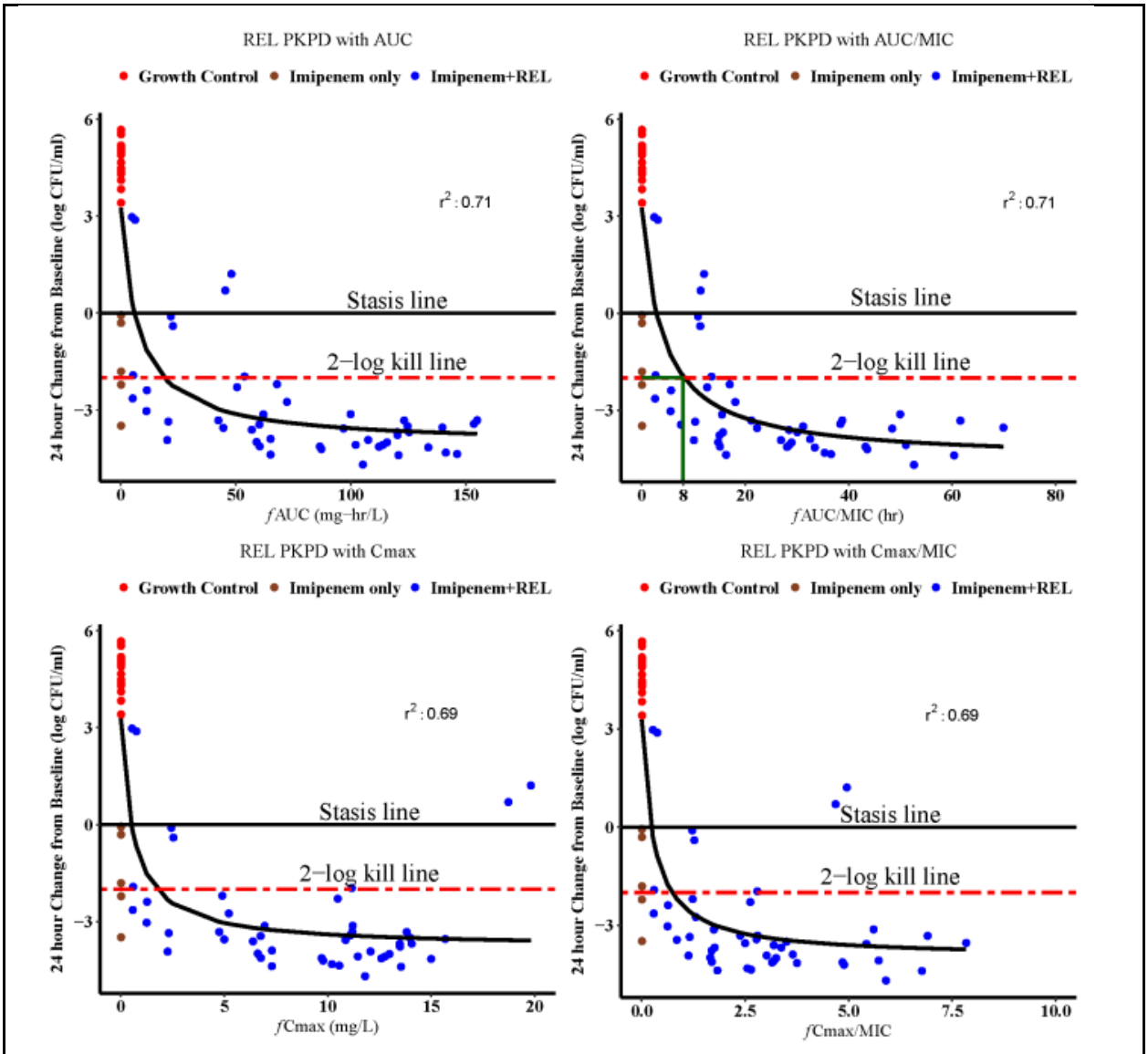
Experiment	P.Aeruginosa	Imipenem	Freq	REL	Freq
HF2012-007	CL5701	200	q6h	50	q6h
HF2012-007	CL5701	200	q6h	200	q6h
HF2012-007	CL5701	500	q6h	250	q6h
HF2012-001	CLB24226	0	q6h	0	q6h
HF2012-002	CLB24226	0	q6h	0	q6h
HF2012-003	CLB24226	0	q6h	0	q6h
HF2012-004	CLB24226	0	q6h	0	q6h
HF2011-008	CLB24226	0	q6h	0	q6h
HF2012-001	CLB24226	500	q6h	0	q6h
HF2012-004	CLB24226	200	q6h	62.5	q3h
HF2012-003	CLB24226	60	q3h	125	q3h
HF2012-002	CLB24226	200	q6h	125	q6h
HF2012-003	CLB24226	200	q6h	125	q6h
HF2012-001	CLB24226	500	q6h	125	q6h
HF2012-002	CLB24226	200	q6h	250	q6h
HF2012-004	CLB24226	200	q6h	250	q12h
HF2012-001	CLB24226	500	q6h	250	q6h
HF2012-002	CLB24226	500	q6h	250	q6h
HF2012-003	CLB24226	500	q6h	250	q6h
HF2012-004	CLB24226	500	q6h	250	q6h
HF2012-004	CLB24226	200	q6h	500	q24h
HF2012-005	CLB24227	0	q6h	0	q6h
HF2012-006	CLB24227	0	q6h	0	q6h
HF2011-001	CLB24227	0	q6h	0	q6h
HF2011-004	CLB24227	0	q6h	0	q6h
HF2011-007	CLB24227	0	q6h	0	q6h
HF2011-004	CLB24227	500	q6h	0	q6h
HF2011-007	CLB24227	500	q6h	0	q6h
HF2012-005	CLB24227	200	q6h	13	q6h
HF2012-006	CLB24227	200	q6h	13	q6h
HF2012-005	CLB24227	200	q6h	27	q6h
HF2012-006	CLB24227	200	q6h	27	q6h
HF2012-005	CLB24227	200	q6h	50	q6h
HF2012-006	CLB24227	200	q6h	50	q6h
HF2012-006	CLB24227	200	q6h	100	q6h
HF2011-004	CLB24227	500	q6h	125	q6h
HF2011-007	CLB24227	500	q6h	125	q6h
HF2012-006	CLB24227	200	q6h	200	q6h
HF2012-005	CLB24227	500	q6h	250	q6h
HF2012-006	CLB24227	500	q6h	250	q6h
HF2011-004	CLB24227	500	q6h	250	q6h

Experiment	P.Aeruginosa	Imipenem	Freq	REL	Freq
HF2011-007	CLB24227	500	q6h	250	q6h
HF2011-011	CLB24228	0	q6h	0	q6h
HF2011-001	CLB24228	0	q6h	0	q6h
HF2011-008	CLB24228	0	q6h	0	q6h
HF2011-011	CLB24228	500	q6h	0	q6h
HF2011-011	CLB24228	500	q6h	125	q6h
HF2011-011	CLB24228	500	q6h	250	q6h
HF2011-001	CLB24354	0	q6h	0	q6h
HF2011-004	CLB24354	0	q6h	0	q6h
HF2011-004	CLB24354	500	q6h	0	q6h
HF2011-004	CLB24354	500	q6h	125	q6h
HF2011-004	CLB24354	500	q6h	250	q6h

Results

Figure 40 shows the exploratory relationship between relebactam exposure metrics and 24 hours change in log10 (CFU) from baseline. The data show an Imax relationship between relebactam concentration and change in log10(CFU). Exposure metrics with the best fit are *f*AUC0-24 (r^2 = 0.71) and *f*AUC0-24/pMIC (r^2 = 0.71). The figure shows that without imipenem treatment, bacteria grows to greater than 3 log10CFU higher compared to baseline. However, the figure also shows that with imipenem only treatment there is significant bacteria killing (up to greater than 3 log10CFU reduction compared to baseline). The greater killing observed with imipenem alone indicate that the tested strains might not be resistant to imipenem. This makes the HIFM unsuitable to evaluate the antibacterial potentiating activity of relebactam. PKPD targets can be derived from **Figure 40**. For *f*AUC0-24/MIC, a PKPD target of about 3 is enough to achieve bacterial stasis and a target of 8 for 2-log kill.

Figure 40. Scatter plots of relebactam exposure metrics versus 24-hour change in log10(CFU) from baseline in Hollow - fiber experiments



Source: Applicant's Translational PKPD Analysis report; page 28 of 159.

Reviewer's comments

The applicant's HF experiments shows substantial killing of the resistant P. aeruginosa strains even when exposed to imipenem alone. The resistant P. aeruginosa strains that show substantial killing by imipenem alone had imipenem MIC that ranges between 8 – 64 mg/L (See Table 99 and Table 100). It is not expected for imipenem alone to have such high bactericidal activity for these resistant strains. This is the major caveat of the applicant's HF experiments and makes the HF data uninterpretable.

The applicant's other analyses utilizing HF data were also unacceptable. The analyzes that were based on hollow-fiber data included: 1) assessment of imipenem exposure versus imipenem bactericidal activity in presence of relebactam; 2) development of a translational PKPD (TPKPD) model which was subsequently used to: determine relebactam Hollow-fiber PKPD driver and

index; simulation exposure-vs-bacterial killing profiles in humans; and predictions of adequate relebactam dose in humans.
The applicant's strategies for development of the TPKPD model were acceptable. The model could have provided a greater understanding of durability of imipenem's antibacterial activity in presence of relebactam while also accounting for development of resistance. However, as stated above the applicant's HF experiments shows substantial killing of the resistant P. aeruginosa strains even when exposed to imipenem alone. This is the major caveat of the applicant's HF experiments and makes the HF data uninterpretable.

1.2.2.4. Simulation of probability of target attainment after Q6H treatment for 1 day

The applicant performed a probability of target attainment (PTA) simulation using relebactam and imipenem PKPD targets determined by experiments described in section 1.2.2.2., and section 1.2.2.4. respectively. In these PTA simulations, imipenem and relebactam concentrations were simulated using parameter estimates of the population PK models described in section 1.1.3. The simulation doses for imipenem and relebactam were based on renal function status as given in Table 101. The simulated concentrations were used to determine %*f*T>MIC for imipenem and *f*AUC0-24/MIC for relebactam. The %*f*T>MIC was defined as percent of time that imipenem concentrations were above the potentiated imipenem MIC during the 6-hour dosing interval. The *f*AUC0-24/MIC was defined as the ratio of relebactam *f*AUC0-24 to potentiated imipenem MIC. A subject was considered to have achieved the treatment-target if both PKPD targets for relebactam and imipenem were attained. The 1-log kill target for relebactam and 2-log kill target for imipenem were 4.3 *f*AUC0-24/MIC and 6.5% *f*T>MIC respectively. The same PKPD targets were applied to P. Aeruginosa and Enterobacteriaceae.

Table 101. Doses of Imipenem and Relebactam Chosen for PTA Simulations

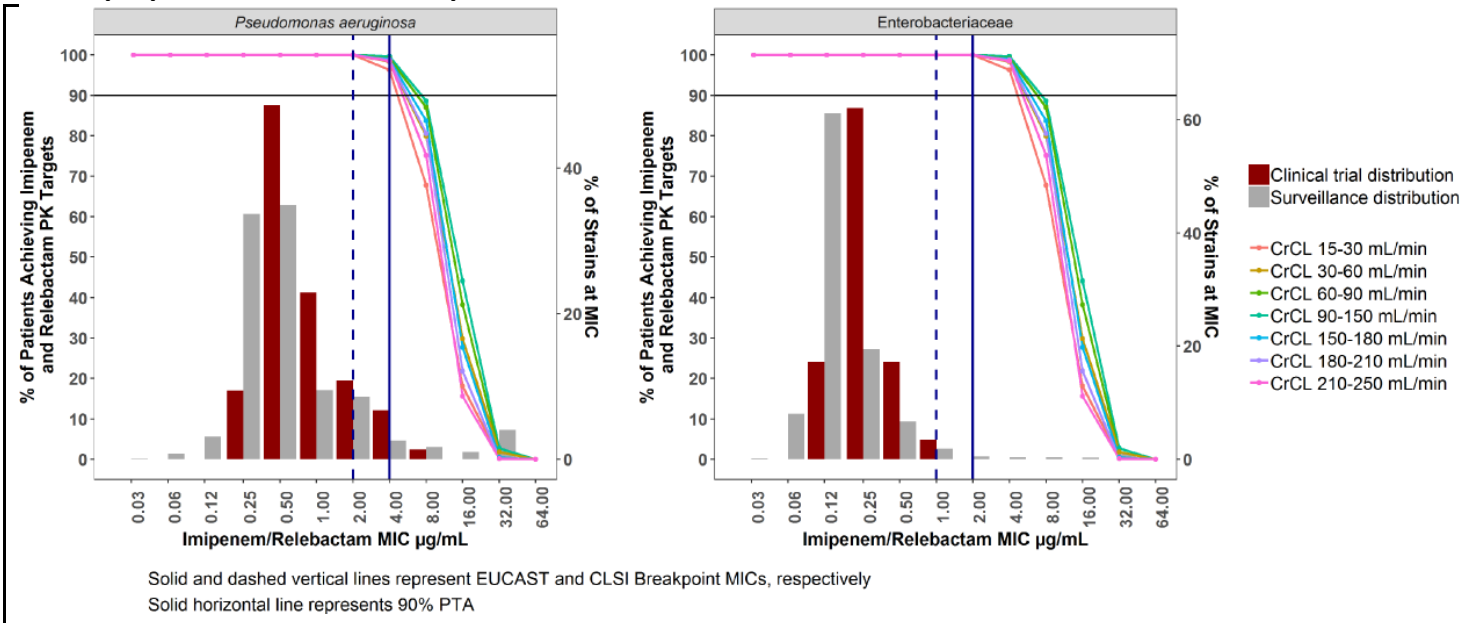
Renal Impairment Category	Creatinine Clearance Range (mL/min)[†]	Dose of Imipenem/Relebactam*
Normal and Augmented Renal Function	90≤CrCL≤ 250	500/250 mg
Mild Renal Impairment	60≤CrCL< 90	400/200 mg
Moderate Renal Impairment	30≤CrCL< 60	300/150 mg
Severe Renal Impairment	15≤CrCL< 30	200/100 mg
End Stage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

Source: Applicant's population Pharmacokinetic report; page 33 of 320

The results from the PTA analyses are given in **Figure 41**. The results show that for *P. Aeruginosa* breakpoint of 4 µg/mL, the population probability of target attainments was greater than 90% regardless of renal functional status. Similarly, for Enterobacteriaceae breakpoints of 2 µg/mL, the population probability of target attainments was greater than 90% regardless of renal functional status.

Figure 41. Percentage of patients achieving imipenem and relebactam targets with P. aeruginosa and Enterobacteriaceae MIC distributions amongst isolates relevant to the proposed indication from phase 2/3 and surveillance data.



Source: Applicant's population pharmacokinetics report; Page 78 of 320

Reviewer's comments

The relebactam PKPD target used by the applicant for PTA analysis was acceptable. However, the imipenem PKPD target was not acceptable as it was based on uninterpretable HF data. Because imipenem's efficacy for susceptible bacteria strains has already been established, it is not necessary to re-evaluate imipenem target-attainment in-vivo.

The reviewer performed an independent PTA analysis to determine relebactam' s probability of target attainment. The target for relebactam was its AUC/pMIC target multiplied by a selected breakpoint. For example, at an imipenem susceptibility breakpoint 2 mg/L, the relebactam target is the selected AUC/MIC target multiplied by 2 mg/L.

Imipenem's breakpoints for P. Aeruginosa and Enterobacteriaceae have already been established. For P. Aeruginosa the breakpoints of 2-, 4-, and 8-mg/L are used in clinics to identify susceptible, intermediately-resistant and resistant strains. For Enterobacteriaceae, the corresponding breakpoints for susceptible, intermediate and resistant strains are 1-, 2-, and 2-mg/L respectively. Therefore, for resistant bacterial strains, choosing imipenem/relebactam breakpoint of 2 mg/L for both P. Aeruginosa and Enterobacteriaceae, the relebactam AUC/MIC target is multiplied by 2 mg/L to obtain the AUC target.

The reviewer investigated relebactam' s probability of attainment of target AUCs at the following AUC/MIC targets: The applicant's determined 1-log kill AUC/MIC target (4.3 mg/L); The reviewer's median (7.5 mg/L) and 97.5th percentile (14.4 mg/L) 1-log kill targets determined from pooled murine-thigh models where imipenem dose levels ranged between 6.25% -99% of human doses. These AUC/MIC targets were multiplied by the breakpoints of 2 to obtain the corresponding AUC targets.

Relebactam's AUCs were simulated using the relebactam population PK model and the applicant's recommended doses in **Table 101**. *The probability of target attainments at different AUC/MIC targets and breakpoints of 2 and 4 are given in* **Table 102**.

Table 102. Percent of patients achieving relebactam AUC targets at AUC/MIC targets of 4.3, 7.5, and 14.4 at breakpoints of 2 and 4 mg/L

	Breakpoints (mg/L)	2			4		
	AUC/MIC targets	4.3	7.5	14.4	4.3	7.5	14.4
Creatinine clearance	< 15 mL/min	100	100	100	100	100	100
	15 - 30 mL/min	100	100	100	100	100	99
	30 - 60 mL/min	100	100	100	100	100	99
	60 - 90 mL/min	100	100	100	100	100	99
	90 - 150 mL/min	100	100	100	100	100	97
	150 - 180 mL/min	100	100	100	100	100	87
	180 - 210 mL/min	100	100	100	100	100	79
	210 - 250 mL/min	100	100	100	100	100	69

The results in Table 100 applies to Enterobacteriaceae if the same relebactam PKPD driver and target are assumed. The applicant's analysis assumed Enterobacteriaceae to have the same relebactam PKPD driver and target as Pseudomonas aeruginosa. However, as the reviewer's analysis indicate, relebactam AUC was a better PKPD driver for Klebsiella pneumoniae, and the target was determined for one resistant strain (KP6755) and found to be 40 mg × h/L (upper bound of the 95% confidence interval was 70 mg × h/L). The probabilities of target attainment in patients with different renal functions for this Klebsiella pneumoniae strain are given in Table 103 below.

Table 103. Percent of patients achieving relebactam AUC targets for Klebsiella Pneumoniae (kp6755)

	AUC target	40 mg×h/L	70 mg×h/L
Creatinine Clearance	< 15 mL/min	100	100
	15 - 30 mL/min	100	93
	30 - 60 mL/min	100	93
	60 - 90 mL/min	100	94
	90 - 150 mL/min	100	90
	150 - 180 mL/min	99	73
	180 - 210 mL/min	97	61
	210 - 250 mL/min	93	50

1.3. References

1. Mavridou E, Melchers RJB, van Mil ACHAM, Mangin E, Motyl MR, Mouton JW. Pharmacodynamics of Imipenem in Combination with β-Lactamase Inhibitor MK7655 in a Murine Thigh Model. Antimicrob Agents Chemother. 2015 Feb;59(2):790–5.

15.5 Additional Clinical Outcome Assessment Analyses

There were no additional clinical outcome assessment analyses conducted.

15.6 Clinical Microbiology Review

15.6.1 Activity in Vitro

Relebactam (REL) is an inhibitor of many Ambler class A and C β-lactamases, but not those of class B (metallo-β-lactamases) and D (OXA). As there are different classifications systems for beta-lactamases based on structural and functional characteristics, this classification system will not be described as such in the imipenem-relebactam labeling. REL can act synergistically with imipenem and reduces the MIC of imipenem for some isolates that are not susceptible (intermediate or resistant) to imipenem . REL does not have antibacterial activity on its own and does not appear to induce AmpC beta-lactamases.

Antibacterial activity

The tables below summarize the in vitro activity against a subset of gram-negative organisms associated with the cUTI and cIAI indications. This analysis included the MIC90 and whether the organisms were also present in the first list of pathogens and the indications and usage section of the imipenem-cilastatin labeling, as REL is being proposed in combination with imipenem (IMI) for this NDA Application. The number of organisms, the in vitro antibacterial activity of isolates taken from the United States, and the relevance of the isolates to the indication were taken into consideration. The information from Study for Monitoring Antimicrobial Resistance Trends (SMART) Surveillance Study 2015-2016 combined is shown in the tables below. The source of the information for Tables 104 and 105 is from study report PD034-MK7655 and PD035-MK7655. The source for the table on anaerobic organisms is from the references 4.3:04XBMT and 4:3:04XBHW.

Table 104: In Vitro Activity of Imipenem-relebactam Against Pathogens Proposed for the Applicant's First List for cUTI

Pathogens	IMI/CIL Label*	N	Surveillance MIC90 Imipenem (mcg/mL)	Surveillance MIC90 IMI/REL (mcg/mL)	MIC Range IMI/REL (mcg/mL)
					(b) (4)
Klebsiella aerogenes	Y	222	1	0.5	≤0.03-≥32
Enterobacter cloacae	Y	522	1	0.25	0.06-1
Escherichia coli	Y	2573	≤0.5	0.25	≤0.03-1
Klebsiella pneumoniae	Y	1398	≤0.5	0.5	≤0.03-4
Pseudomonas aeruginosa	Y	1729	16	2	0.06-≥32

*Yes/No if in the FDA approved labeling for imipenem-cilastatin injection products
Source: Reviewer's table adapted from sources

Table 105: In Vitro Activity of Imipenem-relebactam Against Aerobic Pathogens Proposed for the Applicant's First List for cIAI

Pathogens	IMI/CIL Label	N	Surveillance MIC90 imipenem (mcg/mL)	Surveillance MIC90 IMI/REL (mcg/mL)	MIC Range IMI/REL (mcg/mL)
					(b) (4)
Citrobacter freundii	Y	183	1	0.25	0.06-1

Klebsiella aerogenes	Y	222	1	0.5	≤0.03-≥32
Enterobacter cloacae	Y	522	1	0.25	0.06-1
Escherichia coli	Y	2573	≤0.5	0.25	≤0.03-1
Klebsiella oxytoca	Y	337	≤0.5	0.25	0.06-1
Klebsiella pneumoniae	Y	1398	≤0.5	0.5	≤0.03-4
Pseudomonas aeruginosa	Y	1729	16	2	0.06-≥32

*Yes/No if in the FDA approved labeling for imipenem-cilastatin injection products. SSSI is Skin and Skin Structure Infections
Source: Reviewer's table adapted from sources

Table 106: In Vitro Activity of Imipenem-relebactam Against Anaerobic Pathogens Proposed for the Applicant's First List for cIAI

Pathogens	IMI/CIL Label	N	Surveillance MIC90 Imipenem	Surveillance MIC90 IMI/REL	MIC Range IMI/REL
Bacteroides caccae	Y *Bacteroides* spp.	10	0.5	0.5	≤0.03->32
Bacteroides fragilis	Y *Bacteroides* spp.	220	0.5	0.5	≤0.06-16
Bacteroides ovatus	Y *Bacteroides* spp.	43	1	0.5	0.12-4
Bacteroides stercoris	Y *Bacteroides* spp.	-----	-----	-----	-----

Bacteroides thetaiotaomicron	Y *Bacteroides* spp.	24	2	1	0.125-4
Bacteroides uniformis	Y *Bacteroides* spp.	10	0.25	0.25	0.125-.5
Bacteroides vulgatus	Y *Bacteroides* spp.	12	1	1	0.06-1
Fusobacterium nucleatum	Y	10	0.06	0.06	≤0.03-0.06
Parabacteroides distasonis	Y *Bacteroides* spp.	24	1	1	0.12-4
(b) (4)					

*Yes/No if in the FDA approved labeling for imipenem-cilastatin injection products
Source: Reviewer's table adapted from sources

Reviewer's Comment

(b) (4)

(b) (4) *C. freundii* will be recommended only for the cIAI indication as the approved labeling for imipenem-cilastatin only has *C. freundii* in the indications for cIAI (b) (4)

(b) (4)

(b) (4) The MIC90 for this organism was ≥32 mcg/mL for both imipenem and imipenem-cilastatin in the SMART Surveillance Study 2015-2016.

Table 107 shows the MIC90 data and number of bacteria tested for the proposed second list. The information for gram-positive organisms was taken from study report PD056 MK7655. The other organisms listed were from the study reports as described above

Table 107: In Vitro Activity of Imipenem-relebactam Against Indicated Pathogens in the Applicant's Proposed Second List

Pathogen*	N	MIC90 (mcg/mL) Imipenem	MIC90 (mcg/mL) IMI/REL	MIC Range IMI/REL (mcg/mL)
Staphylococcus aureus (MSSA)	21	0.015-0.03	0.03	≤0.001-0.03
Streptococcus anginosus	30	0.008-0.15	0.03	≤0.001-0.03
Streptococcus constellatus	22	0.008-0.03	0.03	≤0.001-0.03
Achromobacter xylosoxidans	52	≤32	8	0.5-≥32
Citrobacter koseri	104	≤0.5	0.25	0.06-0.5
Enterobacter asburiae	87	1	0.5	0.06-1
(b) (4)				
Eggerthella lenta	11	0.5	0.5	≤0.03-0.5
(b) (4)				
Parvimonas micra	10	0.06	0.06	≤0.03-0.06
Peptoniphilus harei	10	≤0.03	≤0.03	≤0.03
Peptostreptococcus anaerobius	10	0.06	0.06	≤0.03-0.5
Fusobacterium necrophorum	10	2	0.5	≤0.03-0.5
Fusobacterium varium	10	4	4	2-4
Parabacteroides goldsteinii	10	2	2	0.25-4
Parabacteroides merdae	10	8	4	0.05-16
Prevotella bivia	11	0.125	0.125	≤0.03-0.125
(b) (4)				
*Veillonella spp.***	10	1	0.5	0.06-.5

Source: Reviewer's table adapted from sources
*US isolates shown.
** *V. Parvula* is proposed by the Applicant for the second list, but the MIC90 data was provided by the Applicant for *Veillonella* spp.

Reviewer's Comment
The Applicant's in vitro data on the activity of imipenem-relebactam were evaluated for adequacy. The following organisms had sufficient numbers of organisms for inclusion in the second list of the labeling in subsection 12.4: *C. koseri* IMI/REL MIC 0.25mcg/mL (N=104), *E. asburiae* MIC 0.5 mcg/mL (N=87), (b) (4) (b) (4) Of those listed, only *C. koseri* and *E. asburiae* had MICs below the breakpoint proposed for imipenem-relebactam for Enterobacteriacae and so were recommended for the second list of the labeling. For the remainder of the proposed second list organisms in the table above, the organisms were recommended for inclusion in the second list of IMI/REL labeling if the MICs were below the Agency's proposed breakpoints and the organisms were included in the approved labeling for IMI. In doing this analysis, only (b) (4) was additionally removed from the second list. A summary of the labeling recommendations may be found in the clinical microbiology recommendations of this review.

In global surveillance studies of 4597 Enterobacteriaceae, among class A beta-lactamases, CTX-M-1 was the most frequently encountered (N=2231) followed by CTX-M alleles 2, 8, 27, VEB-1, SHV, TEM and KPC-2. GES was the least frequent with 3. Among class C beta-lactamases, AmpC-types were identified by Polymerase Chain Reaction (PCR). CMYII was the most frequently encountered (N=452). Other beta-lactamases encountered were ACT/MIR, DHA, and FOX. Among those Enterobacteriaceae producing class B enzymes, IMP and VIM were the most prevalent (N=5). NDM was the least frequently encountered (N=2).

Additionally, in vitro susceptibility from SMART Surveillance Studies (2015-2016) against 471 US Enterobacteriaceae isolates that expressed EBSL, KPC or AmpC Enzymes was examined. The MIC90 against EBSL-producing isolateswas reportedly ≤0.5mcg/mL for imipenem and 0.25 mcg/mL for imipenem-relebactam. For 53 KPC Enterobacteriaceae the MIC90 was ≥32 for imipenem and 1 for imipenem-relebactam. For 155 AmpC Enterobacteriaceae, the MIC90 was 4 for imipenem and 0.25 for imipenem-relebactam. Among those producing class D alleles, OXA-48 was the most prevalent (N=72).

Reviewer's Comment
The Applicant also included an analysis of imipenem-relebactam enzyme kinetic activity. The half-maximal inhibitory concentration (IC_{50}) of REL for beta-lactamases were as follows: KPC-2 and KPC-3 IC_{50} was approximately 0.2 µM. IC_{50} values for TEM-1, SHV-1, and P99 were as 0.03 µM, 0.03 µM, and 0.13 µM, respectively. IC_{50} values for PDC-1 were 0.47 µM. Additional information on relebactam as an inhibitor is in the mechanism of action section below.

Reviewer's Comment
Care was taken to interpret the data and to describe the studies on molecular characterization of beta-lactamases in labeling. Factors that aid in evading antimicrobial action such as porin

mutations (*OprD*), efflux pumps (MexAB), regulatory genes (*ampD*), and multiple beta lactamases including AmpC were considered. In certain cases, REL was an inhibitor for some beta-lactamase alleles in an enzyme family, but not others. Additionally, some bacterial isolates that contained beta-lactamases were susceptible to imipenem alone. Therefore, although REL has been shown to have inhibition for these beta-lactamases in vitro (TEM, SHV, CTX-M), the potentiation of REL for imipenem activity in the bacteria was not evident.

Data was provided by the Applicant to show the in vitro activity of imipenem-relebactam against Pseudomonas-Derived Cepahalosporinase (PDC)-producing *P. aeruginosa*. PDC is described in the literature as an extended spectrum AmpC (ESAC). It is a mechanism of resistance to some beta-lactams including imipenem. This review focuses mainly on the genotypic characteristics of the bacterial isolates tested. Language is provided in the labeling that describes how there may be varying levels of expression, amino acid variations or other resistance mechanisms not yet identified among the bacterial isolates tested.

Relebactam reduced the MIC of imipenem in vitro, but not to levels of susceptibility in all cases. In imipenem-relebactam clinical trials *P. aeruginosa* and Enterobacteriaceae isolates were characterized molecularly, including isolates that were characterized genotypically for PDC, beta lactamases, and OprD porin status. (b) (4)

(b) (4)

Time Kill

Time kill analysis was conducted to monitor the in vitro bactericidal activity of imipenem in the presence and absence of relebactam. *P. aeruginosa* strains CL5701 and CLB24228, imipenem resistant strains were used. MICs for these isolates were 16 mcg/mL and 32 mcg/mL, respectively. The addition of relebactam restored activity of imipenem.

In vitro hollow fiber PK/PD studies were also used to evaluate the efficacy of the two doses used in PN003 and PN004 trials against imipenem-resistant *P. aeruginosa* and *K. pneumoniae*. A study by Hirsch et al.; 2012, described 4 imipenem-nonsusceptible isolates: KPC-2-producing *K. pneumoniae* isolates KP6339 and 3 *P. aeruginosa* isolates PA24226, PA24227, and PA24228, with OprD porin deletions and overexpression of AmpC. The combination of imipenem and relebactam reduced the bacterial burden at 24 hours and suppression of bacterial growth was observed with the exception of PA24226. In the case of PA24228, sustained suppression was only seen after a dose increase to 1000 mg.

In study PD031, 15 imipenem-resistant Enterobacteriaceae and *P. aeruginosa* were tested in the in vitro PK/PD hollow fiber cell culture system. Activity was tested against the *P. aeruginosa* strains CLB 24227, CLB 24228, and CLB 24226, with imipenem MIC values of 16 to 32 mcg/mL, and *Enterobacteriaceae* strains, including the KPC-producing *K. pneumoniae* strain CL6339 (imipenem MIC 64 mcg/mL). An exception was the *P. aeruginosa* strain CLB 24354 with an imipenem MIC value of 64 mcg/mL (imipenem/REL MIC, 16 mcg/mL). For CLB 24354, the 125 mg q6h dose of REL in combination with imipenem demonstrated initial killing followed by regrowth, resulting in suboptimal efficacy. Sustained killing for the full 70-hour incubation

period with a 4-log kill was maintained at the 250 mg REL q6h dose in combination with 500 mg imipenem q6h. The adequacy of the dose in these studies has been investigated by the FDA clinical pharmacology team. See the Clinical Pharmacology review of this document for additional information.

In study PD033, the antibacterial effect if imipenem-relebactam was studied against Enterobacteriaceae and *P. aeruginosa* using the in vitro hollow fiber system for more than 168 hours. One wild-type *E. coli* strain (46961, Southmead collection), three *K. pneumoniae* strains, and four strains of *P. aeruginosa* were used. Imipenem MIC values were determined in the presence of 4 mcg/mL REL. Imipenem/REL produced a reduction in viable colony-forming units (CFU)/mL for Enterobacteriaceae of 4.23 ± 0.32 and 4.35 ± 0.21 log CFU/mL at 24 hours and 168 hours, respectively. The Enterobacteriaceae strains were killed, with the wild type *E. coli* strain and *K. pneumoniae* 42421 (KPC) were eradicated from the model by 6 hours. The other KPC-producing strain *K. pneumoniae* 62267 was eliminated by 24 hours and the AmpC- producing strain with porin loss (*K. pneumoniae* 47929) was eradicated by 96 hours.

Against *P. aeruginosa* imipenem/REL produced bacterial killing, eradicating an isogenic mutant from the model and suppressing bacterial counts over 168 hours for the other strains. The *P. aeruginosa* strains all demonstrated a 3- to 4-log reduction in bacterial count by 6 hours; however, only one strain was eradicated from the model, *P. aeruginosa* 17286 (an isogenic mutant) which was eliminated from the model by 96 hours. For 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 hours to 3 to 4 $\log_{10}$ at 168 hours. None of this regrowth demonstrated increases in imipenem/REL MIC values. An extended (14 day) imipenem/REL simulation with an AmpC OprD-producing *P. aeruginosa* strain produced some changes in the population profile with changes in progeny MIC values. Not all of the isolates recovered at 14 days exhibited increased MIC values to imipenem/REL. Addition of a second agent (amikacin) in the 14-day model suppressed regrowth.

Additional isolates used the hollow fiber experiments and a summary of the results are shown in Table 108 below:

Table 108: Bacterial Isolates Used in Applicant's Hollow Fiber Experiments

Organism	Isolate Number	Imipenem MIC (µg/mL)	Imipenem MIC in presence of 4 µg/mL Relebactam (µg/mL)	β-lactamase	Hollow Fiber Results	
					125 mg Relebactam	250 mg Relebactam
Pseudomonas aeruginosa	CLB 24227	16	2	blaPDC-35	> 4 log kill with no regrowth up to 70 hr	> 4 log kill with no regrowth up to 70 hr
Pseudomonas aeruginosa	CLB 24354	64	16	blaPDC-3	Regrowth starting at 6 hr	> 4 log kill with no regrowth up to 70 hr
Pseudomonas aeruginosa	CLB 24228	32	8	blaPDC-16	> 4 log kill with no regrowth up to 70 hr	> 4 log kill with no regrowth up to 70 hr
Pseudomonas aeruginosa	CLB 24226	32	4	blaPDC-19	> 4 log kill with no regrowth up to 70 hr	> 4 log kill with no regrowth up to 70 hr
Klebsiella pneumoniae	CL 6339	64	1	KPC-2, TEM, SHV	> 4 log kill with no regrowth up to 70 hr	> 4 log kill with no regrowth up to 70 hr
Klebsiella pneumoniae	CL 6569	256	4	KPC-2	ND	> 4 log kill with no regrowth up to 70 hr
Klebsiella pneumoniae	CLB 26410	> 256	8	KPC-2	ND	> 4 log kill with no regrowth up to 70 hr
Klebsiella pneumoniae	CL 5763	32	0.5	KPC-3	ND	> 4 log kill with no regrowth up to 70 hr
Klebsiella pneumoniae	CL 6838	16	0.5	KPC-3	ND	> 4 log kill with no regrowth up to 70 hr
Escherichia coli	IHMA 1224137	8	≤ 0.5	TEM-OSBL, CTX-M-14, CMY-140	ND	> 4 log kill with no regrowth up to 70 hr
Escherichia coli	IHMA 1231530	4	0.5	CTX-M-15, CMY-2	ND	> 4 log kill with no regrowth up to 70 hr
Klebsiella pneumoniae	IHMA 516426	16	0.5	CTX-M-14, DHA	ND	> 4 log kill with no regrowth up to 70 hr
Serratia marcescens	IHMA 1203541	8	1	CTX-M-3	ND	> 4 log kill with no regrowth up to 70 hr
Klebsiella oxytoca	IHMA 1211369	32	0.25	KPC-6	ND	> 4 log kill with no regrowth up to 70 hr
Klebsiella pneumoniae	IHMA 520284	16	0.25	KPC-11	ND	> 4 log kill with no regrowth up to 70 hr

blaPDC = chromosomally encoded AmpC (class C); CMY = cephamycins β-lactamase CTX-M = cefotaxime hydrolyzing capabilities β-lactamase; DHA = Dhahran Hospital; hr = hours; KPC = class A serine Klebsiella pneumoniae carbapenemase; µg/mL = microgram per milliliter; MIC = minimum inhibitory concentration; REL = relebactam or MK-7655; ND = not determined/not performed; SHV = sulfhydryl variable β-lactamase; TEM = Temoneira β-lactamase

Source: This submission.

Reviewer's Comment
Some isolates used in the hollow fiber experiment did not provide evidence of the contribution of relebactam to the combination product. *E. coli* strain IHMA 1231530 and *S. marcescens* strain IHMA 1203541 exhibited the same CFU reductions for REL 250 mg + IMI 500 mg as IMI 500 mg alone. *K. pneumoniae* strain IHMA 516426 exhibited the same CFU reductions for REL 250 mg + IMI 500 mg as IMI 500 mg alone. However, relebactam inhibited bacterial regrowth after 24 hours. It is likely that these strains contained beta-lactamases that were not of the type that relebactam has inhibitory activity against. See the Agency's clinical pharmacology review and the clinical microbiology summary for additional information.

Post-antibiotic and Post-inhibitor Effect
The post-antibiotic effect (PAE) is the ability of an antimicrobial agent to suppress growth of target pathogens after a brief *in vitro* exposure period to supra-inhibitory concentrations of the agent followed by its subsequent removal. The Post-inhibitor effect (PIE) is the combined effect of continued inhibition of the beta-lactamase after removal and sub-inhibitory concentrations of the beta-lactam antibiotic. In study PD016, the PAE and PIE of imipenem-relebactam were evaluated against an imipenem-resistant isolate of *P. aeruginosa,* CL5701. Time-kill analysis showed that imipenem was bactericidal at 4-fold and 2-fold the MIC (16 mcg/mL). Imipenem was also bactericidal at 0.25-fold the MIC (4 mcg/mL) when combined with 4, 8, or 16 mcg/mL REL.

Following initial exposure at 1-fold, 2-fold, and 4-fold the MIC, imipenem alone resulted in PAE from 1 to 3 hours against the evaluated isolate. A similar PIE was also observed with initial exposure to imipenem at 0.25-fold the MIC (4 mcg/mL) when combined with 4, 8, or 16 mcg/mL REL. In contrast, the PAE observed following initial exposure to the sub-inhibitory concentration of 4 mcg/mL imipenem alone was similar to the unexposed growth control. When cells were maintained in 4 mcg/mL imipenem and pre-exposed to 4, 8, or 16 mcg/mL REL, growth was inhibited for 4 to 6 hours relative to controls. In other words, cells unexposed to REL but grown in the presence of 4 mcg/mL imipenem. REL was able to result in a prolonged PIE and was bactericidal when combined with imipenem at 4 mcg/mL against the evaluated imipenem-resistant *P. aeruginosa* CL 5701.

In Study PD018, the PAE effect of REL in various combinations with imipenem was evaluated against *P. aeruginosa* CL 5701 with REL (at 2, 4, 8, and 16 mcg/mL) combined with 4 mcg/mL imipenem during the exposure period, followed by re-constitution in Cation-adjusted Mueller-Hinton broth containing sub-inhibitory (4 mcg/mL) imipenem. This demonstrated a longer PAE (4.7 to 5.3 hours) than re-constitution without imipenem (0.6 to 2.6 hours) for all REL concentrations tested. The presence of REL during the exposure period had a greater effect than sub-inhibitory imipenem alone.

PAE was also studied in *P. aeruginosa* CLB 24228, an AmpC-inducible strain. CLB24228 had an imipenem MIC of 64 mcg/mL and an Imipenem-relebactam MIC of 16 mcg/mL in the presence of 4 mcg/mL REL. For CLB 24228 the differential between incubation with imipenem at 4 mcg/mL plus REL at 16, 8, or 4 mcg/mL vs. continuous incubation with imipenem at 4 mcg/mL yielded PIE values of 2.4 hours, 0.1 hours, and 2.0 hours, respectively. The PIE for CL 5701 was longer than that for CLB 24228. The length of the PAE and PIE may be affected by the differences in strains and/or experimental methods.

15.6.2 **Mechanism of Action**

The mechanism of action of imipenem, a carbapenem antibacterial drug, has been described in FDA approved labeling for imipenem-cilastatin injection products. The mechanism involves the binding and inhibition of certain penicillin binding proteins leading to inhibition of bacterial cell

wall synthesis. Relebactam is being proposed by the Applicant for use in combination with imipenem as a beta lactamase inhibitor. It is described as a slowly-dissociating inhibitor of Ambler class A and class B beta lactamases. It does not have intrinsic activity for the bacterial pathogens tested in the NDA submission. The evidence provided by the Applicant suggests that relebactam enhances the activity of imipenem on some imipenem-susceptible bacteria by inhibiting certain beta-lactamases. See in vitro activity above for additional information on the types of beta-lactamases inhibited by relebactam. The inhibition profile of relebactam and comparators is shown in Table 109 below:

Table 109: Inhibition Profile of Marketed Beta-Lactamase Inhibitors Compared to REL (Half-Maximal Concentrations)

Enzyme	Source	Clavulanic acid[a]	Sulbactam[a]	Tazobactam[a]	REL[a]
TEM-1 (Class A)	*E. coli*	0.026	1.125	0.012	0.031
KPC-2 (Class A)	*K. pneumoniae*	5.1	33	43	0.208
KPC-3 (Class A)	*K. pneumoniae*	5.4	52	27	0.197
SHV-1 (Class A)	*K. pneumoniae*	0.012	5.5	0.067	0.029
SHV-5 (Class A)	*K. pneumoniae*	0.0012	0.058	0.007	0.361
IMP-1 (Class B)	*P. aeruginosa*	> 20	> 200	> 200	> 50
ADC-1 (Class C)	*Acinobacter baumannii*	> 500	39	18	4.063
PDC-1 (Class C)	*P. aeruginosa*	> 500	14	1.491	0.465
P99 (Class C)	*Enterobacter cloacae*	> 250	27	12	0.134
OXA (Class D)	*Acinobacter baumannii*	28	> 500	58	> 50
CTX-M15 (Class A)	*E. coli* K12	Not determined	Not determined	Not determined	0.782
GES-2 (Class A)	*P. aeruginosa*	Not determined	Not determined	Not determined	0.087
OXA-48 (Class D)	*K. pneumoniae*	Not determined	Not determined	Not determined	130.5
NDM-1 (Class B)	*K. pneumoniae*	Not determined	Not determined	Not determined	> 10
VIM-1 (Class B)	*K. pneumoniae*	Not determined	Not determined	Not determined	> 10

a The half-maximal inhibitory concentrations (IC_{50} values) are presented in micromolar.

ADC-1 = *Acinetobacter*-derived cephalosporinases, class C β-lactamase; BLI = β-lactamase inhibitor(s); CTX-M15 = class A β-lactamase with greater activity against cefotaxime than other oxyimino-β-lactam substrates; GES-2 = class A Guiana extended-spectrum β-lactamase with increased hydrolysis of imipenem; IMP-1 = imipenem-hydrolyzing carbapenemase, class B metallo-β-lactamase; KPC-2 = *Klebsiella pneumoniae* carbapenemase β-lactamase-2; KPC-3 = *Klebsiella pneumoniae* carbapenemase β-lactamase-3; NDM-1 = New Delhi class B metallo-β-lactamase; OXA = oxacillinase; OXA-48 = OXA-type β-lactamase; P99 = P99 β-lactamase; PDC-1 = Ampicillin class C β-lactamase from *Pseudomonas aeruginosa*; SHV-1/SHV-5 = Bacterial non-metallo-β-lactamases; TEM-1 = a bacterial non-metallo-β-lactamase; VIM-1 = Verona integron-encoded class B metallo-β-lactamase

Source: Report PD002 [Sec. 2.6.3.1]

Reportedly, the reaction mechanism of relebactam includes an acylation in the order of minutes and a slow deacylation of the enzyme/inhibitor complex. The target engagement time is described in the order of greater than 1 hour for KPC and greater than 6 hours for KPC-2. The inhibition potency (Ki) for relebactam for PDC (68nM), ADC (37nM), KPC-2 (14 nM), KPC-3 (14 nM), TEM-1 (4.2 nM) and CTX-M-15 (5.6 nM) were provided and the upper limit of the dissociation rate ranged from 10^{-2} (k2, per sec) with PDC-1 to 10^{-4} (k2, per sec) for TEM-1.

Resistance

There is no known cross-resistance with other classes of non-beta-lactam antimicrobials. Resistance mechanisms of beta-lactam drugs in gram-negative bacteria have been described in the literature and in FDA-approved labeling for the beta lactam class of drugs to include the production of beta-lactamases, up-regulation of efflux pumps, and loss of outer membrane porins. During efflux studies, the Applicant did not observe evidence that imipenem and or relebactam are subject to efflux. The Applicant also studied imipenem-relebactam activity against isolates of *P. aeruginosa* that over produced efflux pumps in an *OprD* and *MexT* mutant background.

Based on results of frequency of resistance testing conducted with varying concentrations of imipenem combined with REL against clinical isolates of *P. aeruginosa* (N=4) and *K. pneumoniae* (N=5), the Applicant stated that the spontaneous resistance against imipenem/REL is anticipated to occur at a very low frequency among *Pseudomonas* species and most KPC-expressing *Klebsiella* species

To determine the frequency of resistance, and select resistant mutants, an efficiency of plating (EOP) was performed. A Luria-Delbruck fluctuation test was also done for one strain to measure the rate of resistance per cell generation. Concentrations were based around 4 mcg/mL imipenem (the breakpoint at the time). *P. aeruginosa* isolates CL5701 and CLB 24228 and K. *pneumoniae* (expresses KPC) isolates CL6339 and CL6569 were tested.
Of the four strains tested in study set 1, only *K. pneumoniae* CL 6569 (KPC-expressing strain) had an average resistance frequency of 2×10^{-7} among the three concentrations tested. The resistance frequency did not vary more than 4-fold between the concentrations. When 17 of the resultant mutants were analyzed, a majority exhibited both increased MIC values to imipenem as well as requiring higher concentrations of REL to synergize to the susceptibility breakpoint. For this strain background, all of the selected mutants were synergized to imipenem breakpoint by 32 mcg/mL or less (range 8 to 32 mcg/mL) of REL vs. 4 mcg/mL for the parent. The mechanism underlying this resistance is unknown; however, no differences between the selected mutant and parent strain were observed by the Applicant for beta-lactamase expression, beta-lactamase induction by imipenem, or REL inhibition of beta--lactamase activity in lysates.

In study set 1, no mutants resistant to the combination of imipenem/REL were obtained for three of four isolates tested. For the one isolate where a minor proportion of the mutants obtained required > 16 mcg/mL REL to restore susceptibility to imipenem, selection using

higher concentrations of REL or at higher concentrations of imipenem in the combination yielded no resistant mutants. In the second set of resistance selection experiments (study set 2), 3 isolates of *P. aeruginosa* and 4 isolates of *K. pneumoniae* were examined for resistance frequency by EOP methods. One isolate of *P. aeruginosa* (CL 5701) and one isolate of *K. pneumoniae* (CL 6339) were repeated from study set 1.

In vitro selection for resistance was conducted in 9 clinical isolates of *P. aeruginosa* and Enterobacteriaceae producing class A or C enzymes, including KPC. In one isolate, a *K. pneumoniae* expressing a KPC-2 with a very high MIC to imipenem, resistant isolates were selected but the mechanism of resistance was not confirmed by whole genome sequencing. For two other KPC-expressing Enterobacteriaceae, mutants could be selected at 4× the breakpoint concentration of imipenem (breakpoint concentration was 1 mcg/mL) combined with 4 mcg/mL REL. However, for one of these isolates in hollow fiber studies, no increase in growth was seen for up to 72 hours even at concentrations of REL one-half the clinical dose. For other KPC-expressing Enterobacteriaceae no resistant mutants were selected. Among *P. aeruginosa* isolates mutants arose at a frequency of 3×10^{-9} at 48 hours with one isolate, while with two others no mutants arose.

Reviewer's Comment
Based on the Applicant's results of studies on resistance, resistance selection against imipenem/REL did not occur at a high frequency among most bacterial isolates tested. The highest frequency of resistance was for *K. pneumoniae* CL 6569, a KPC producing strain, at a frequency of approximately 2×10^{-7} as an average among three concentration paradigms tested including 2 times the MIC of IMI and REL each.

Susceptibility Test Methods and Interpretive Criteria
In the Applicant's studies, MIC values were generally consistent among different laboratories, and the addition of REL appeared to have no effect on the reliability of microbiological test methods. Standard methodologies and QC studies were used to identify QC ranges, which were approved by the CLSI for both broth microdilution and agar dilution (anaerobes only) for a variety of QC organisms. Susceptibility testing was not anticipated to present technical issues.

Effect of Laboratory Testing Conditions on Imipenem-relebactam Activity in Vitro
Determination of in vitro susceptibility concentration of REL
The fixed 4 mcg/mL in vitro susceptibility concentration of REL was determined from the average concentration (Cavg) of REL when dosed as 250 mg every 6 hours in humans. Susceptibility testing for imipenem/REL was therefore performed with a fixed REL concentration of 4 mcg/mL. The 4 mcg/mL concentration was used to distinguish between imipenem/REL-susceptible gram-negative isolates that express beta-lactamases inhibited by REL from those that are not (i.e., class B and D beta-lactamases).

Other manual tests that have been developed for imipenem-relebactam susceptibility testing include Thermofisher Trek Sensititre™ 96 well plate and two gradient diffusion MIC strips developed by Liofilchem, Inc. Automated MIC testing was by bioMérieux (VITEK® 2), Beckman Coulter (MicroScan) and Becton Dickinson (Phoenix™).

Susceptibility Testing Conditions for Imipenem-relebactam
The effect of standard conditions on imipenem/REL MICs was compared to the impact of nonstandard conditions (testing in the presence of serum, altered pH, high/low inoculum, varied cation concentration, addition of polysorbate, and incubation in 5% carbon dioxide). Media age was also examined for target pathogens (beta-lactamase producing and non-producing *E. coli, K. pneumoniae*, and *P. aeruginosa* [Ref. 4.2.1.1: PD013MK7655; [Ref. 4.2.1.1: PD015MK7655]. Nearly all of the evaluated parameters had no or minimal impact (i.e. MIC values within one-doubling dilution relative to standard conditions) on imipenem/REL activity against *E. coli*, *K. pneumoniae*, and *P. aeruginosa* across the range of REL concentrations that were evaluated. The exception was a trend towards increased MIC values at low pH. The Applicant reported that this trend was evident for both imipenem alone and imipenem/REL and hypothesized that the effect was due to the instability of imipenem at low pH.

Determination of Appropriate Disk Mass
The ability to determine bacterial susceptibility to imipenem-relebactam using CLSI reference methods was evaluated in a series of studies. These studies included the determination of the appropriate imipenem-relebactam disk mass for disk diffusion assays, comparison of MICs determined by broth microdilution or agar dilution test methods, the effect of modification of test parameters on MICs, and the quality control ranges for reference strains used to control test methods.

Positive disk diffusion results were first established with REL applied to manufactured imipenem disks. Disk mass was determined in three studies, one with a range of REL concentrations (5, 10, 15, 20, 25, and 30 mcg, Report PD012 – MK-7655) added to commercial disks of imipenem (10 mcg); a second study where four disk masses of REL were compared (10, 15, 20, and 25 mcg, Report PD028 – MK-7655), and a third study focused on two masses (20 and 25 mcg, Report PD027 – MK-7655). The stability of disks was confirmed after short-term storage under refrigeration (report PD011-MK7655). For the PN003, PN004 and PN013, disk diffusion was also conducted for all pathogens using an imipenem/REL 10/25 mcg disk produced by Mast Group Ltd. (Bootle, UK).

Reviewer's Comment
The Applicant's evaluation of laboratory conditions which affect imipenem-relebactam activity in vitro were provided. The effect of activity in urine was not described. Among the conditions tested there was consistency of results with the exception of low pH conditions. MAST imipenem/REL 10/25 mcg disk was used in the clinical trials.

Quality Control for Susceptibility Testing
Studies conducted to establish QC ranges for the in vitro susceptibility testing of imipenem-relebactam were performed by the Applicant in accordance with guidelines established by CLSI (CLSI M23). Tier 2 multi-laboratory studies (9 laboratories) were used to establish quality control ranges QC ranges for microbroth dilution. Quality control parameters have been accepted by CLSI (2017) for imipenem-relebactam for the following strains (BMD is for broth microdilution, and AD for agar dilution below):

Klebsiella pneumoniae ATCC 700603 (ESBL producer: SHV-18; BMD only), *Klebsiella pneumoniae* ATCC BAA-1705 (KPC producer: KPC-2, TEM-1, SHV-11; BMD only), *Klebsiella pneumoniae* ATCC BAA-2814 (B21/KP1074) (KPC producer: KPC-3, TEM-1, SHV-11; BMD only), *Streptococcus pneumoniae* ATCC 49619 (BMD only), *Bacteroides fragilis* ATCC 25285 (BMD and AD), *Bacteroides thetaiotaomicron* ATCC 29741 (AD only), and *Eggerthella lenta* ATCC 43055 (AD only).

CLSI has published a footnote that data from only one disk manufacturer was used for the development of CLSI recommended QC ranges as data from other manufacturers was not available at the time. Beta-lactamase producing quality control isolates were used in the analysis as well.

Reviewer's Comment
The Quality Control tier 2 testing described by the Applicant above was done according to CLSI guidelines and had a high percentage of quality control results that were in range . Quality Control Ranges have been published by the CLSI in M100-S28 for MIC and disk for aerobic bacteria and agar and broth methods for anaerobic bacteria. This reviewer recommends the Quality Control published by the CLSI in M100 and that the published quality control values and isolates are referenced on the Agency's breakpoint website.

Antibacterial Interactions
The potential interactions between imipenem-relebactam and other agents (e.g. synergy, antagonism, indifference) were not investigated by the Applicant.

15.6.3 **Activity in Vivo (Animal Studies)**

Consistent with the in vitro studies, REL has the ability to restore the antibacterial activity of imipenem in vivo against isolates that are not susceptible to imipenem. In vivo models also suggest that REL penetrates pulmonary ELF. Several animal models of infection in neutropenic mice were utilized for determining the in vivo efficacy of REL co-administered with IMI.

In preliminary studies [Ref. 4.2.1.1: PD006MK7655], treatment followed shortly after infection (disseminated infection with *P. aeruginosa* or *K. pneumoniae* and intranasal infection with *P. aeruginosa*). IMI in combination with REL was also studied in a different model which the Applicant termed a delayed therapy model of infection with *P. aeruginosa.* In this model, treatment initiated after the infection was established. Further studies also used the organisms studied in the delayed-treatment pulmonary infection model [Ref. 4.2.1.1: PD040MK7655].

REL demonstrated the ability to restore the antibacterial activity of imipenem against some imipenem intermediate or resistant isolates in vivo. Isolates of *P. aeruginosa* and Enterobacteriaceae expressing beta-lactamases that contribute to imipenem resistance were rendered susceptible to imipenem.

Reviewer's Comment
As the PN013 clinical trial data was minimal for this NDA, information pertaining to the animal models were discussed internally at the Agency and a summary of the data was included in subsection 12.4 of the labeling.

The susceptibilities (MIC range) of isolates used in the animal infection models is shown in the table below:

Table 110: Animal Models of Infection Used to Test the Effect of Relebactam on the in Vivo Efficacy of Imipenem

Animal Model	Organisms (N)	β-Lactamase	Species	MIC Imipenem (µg/mL)	MIC Imipenem/REL (µg/mL)	Dosing
Murine delayed lung	Clinical isolates (10)	PDC-1, PDC-3, PDC-5, PDC-8, PDC-16, PDC-35, PDC-36	*P. aeruginosa*	16 – 64	4 – 16	Sub-efficacious for imipenem
Murine delayed lung	Clinical isolates (2)	KPC-2, KPC-3	*K. pneumoniae*	64	0.25 – 0.50	Sub-efficacious for imipenem
Murine thigh	Clinical isolates (5)	PDC-5, PDC-8, PDC-16, PDC-19, PDC-35	*P. aeruginosa*	16 – 64	≤ 1 – 1	Sub-efficacious and humanized for imipenem
Murine thigh	Clinical isolates (2)	KPC-2, KPC-3	*K. pneumoniae*	2 - 64	2 - 16	Sub-efficacious and humanized for imipenem

Source: [Ref. 4.2.1.1: pd006mk7655, pd040mk7655, pd017mk7655] [Ref. 5.4: 04M693]

The table above shows some of the virulence factors of the isolates tested.

Reviewer's Comment
Two imipenem-resistant clinical strains were used in study PD006: *P. aeruginosa* strain CLB 24228 had an imipenem MIC of 32 mcg/mL which is reduced to 8 mcg/mL in the presence of 4 mcg/mL MK-7655; and *K. pneumoniae* strain CL 6339 expressed the KPC-2 carbapenemase-hydrolyzing enzyme and had an imipenem MIC of 64 mcg/mL, which was reduced to 4 mcg/mL in the presence of 2 mcg/mL of MK-7655. That *P. aeruginosa* strain harbors an over-expressed

AmpC and lacks the OprD porin. This is described in the literature as a primary mechanism of resistance for imipenem in *P. aeruginosa*. The beta-lactamases produced by the isolates used in the animal models is shown in the table above.

Studies PD006 and PD040 used sub-therapeutic doses of imipenem at 5 mg/kg. See clinical pharmacology section of this review for additional information. Study PD017 was an exploratory analysis of the relationship between in vitro and in vivo efficacy and is not discussed in this section of the review.

Reviewer's Comment
While the animal models used for determination of efficacy included lung models which are not as relevant for the indications of cUTI and cIAI as other animal models such as the murine pyelonephritis model for UTI, the animal models were useful. They provided data for proof of concept, evidence of the contribution of the components to the activity of the combination product, and some animal models were useful to clinical pharmacology to determine PK/PD targets and population PK models.

Bacterial isolates used in the delayed treatment models are shown in the table below:

Table 111: Bacterial Isolates Used in Delayed Treatment Models

Organism	Species	Imipenem Minimum Inhibitory Concentration (µg/mL)	Imipenem/REL Minimum Inhibitory Concentration (µg/mL)
CL 5701	*Pseudomonas aeruginosa*	16	2
CLB 24228	*Pseudomonas aeruginosa*	32	8
CLB 24385B	*Pseudomonas aeruginosa*	64	16
CLB 24427	*Pseudomonas aeruginosa*	16	8
CLB 25005A	*Pseudomonas aeruginosa*	32	8
CLB 25649	*Pseudomonas aeruginosa*	64	16
CLB 25677	*Pseudomonas aeruginosa*	64	8
CLB 25893	*Pseudomonas aeruginosa*	64	16
CLB 26735	*Pseudomonas aeruginosa*	64	16
487710	*Klebsiella pneumoniae*	64	0.25
515744	*Klebsiella pneumoniae*	64	0.5
µg/mL = microgram per milliliter; REL = relebactam			

Source: This submission.

15.6.4 Pharmacokinetics/Pharmacodynamics

PK of REL and imipenem were studied in clinical pharmacology studies and were also characterized using a population PK model. The clinical pharmacology team assessed whether the joint PTA assessment for REL and imipenem supported the proposed dose/dose adjustments for IMI and REL and whether it was adequate to meet PK/PD targets and provide

efficacy including for imipenem-resistant bacterial strains. REL exposure-response relationship was investigated by simulating the bacterial kill against increasing REL doses, keeping imipenem constant at 500 mg every 6 hours in the background.

PK/PD Models In Vivo
In vivo neutropenic mice models were used by the Applicant to evaluate the PK/PD driver for REL. *P. aeruginosa* and *K. pneumoniae* strains were studied. Subtherapeutic doses of imipenem were used (< 500 mg). The Applicant determined that AUC/MIC was the PK/PD driver for REL.

Reviewer's Comments
The Agency's clinical pharmacology review team determined the Applicant's PTA inadequate to support the breakpoints. See clinical pharmacology section for additional information on the Agency's assessment of the PTA. The Agency's proposed breakpoints are also further discussed in the clinical microbiology recommendations section of this review.
This application relies on a limited clinical program. Non-clinical data and PTA simulations using clinical PK data were pivotal in dose selection. REL 250mg was shown to restore the activity of imipenem (in isolates that are not susceptible to imipenem) when combined with 500 mg imipenem in a hollow fiber infection model (PD031).

15.6.5 Clinical Microbiology Analyses of Efficacy

IMI/REL has been studied in three clinical trials, one in subjects with cIAI (PN004), one in subjects with cUTI (PN003) and a third clinical trial in subjects with infections caused by isolates that are not susceptible to imipenem (PN013). In these trials, microbiological data were collected from infected patients.

Bacterial pathogens isolated from infection sites and blood samples were sent to a central microbiology laboratory. The central microbiology laboratory for PN003 and PN004 was (b) (4) The central microbiology laboratory for the PN013 study was (b) (4) (b) (4)

Isolates were identified to the species level using 2 methodologies: VITEK® 2 (biochemical testing) for identification of bacterial strains received from sites in Eurasia, and Bruker Biotyper® (matrix assisted laser desorption/ionization-time-of-flight [MALDI-TOF] mass spectrometry) (Bruker Daltronics, Bremen, Germany) for identification of bacterial strains received from sites in the Americas and Asia (biochemical testing was also used as a backup method of identification). Susceptibility testing was done by broth microdilution according to CLSI document M07-A10.

(b) (4) performed QC testing with one or more QC isolates each day that trial isolates were tested. Testing was concurrent with the PN003 and PN004 clinical trials; however, QC ranges were not available for imipenem/REL at the time of the concurrent testing.

Nearly 100% of quality control values were within current CLSI established ranges [Ref. 5.4: 04ZX8X]. Six (6) values were out of range using now accepted QC ranges for imipenem/REL.

Microbiological Evaluations in Clinical Trials (PN003, PN004 and PN013)

PN003 (cUTI)
Quantitative urine cultures were performed at each site's local laboratory within 48 hours prior to enrollment. In order to be eligible for participation, presence of pyuria and a positive urine culture were required. To support evaluation of microbiological response, additional urine cultures were collected at subsequent trial visits; unscheduled samples were also collected when there was clinical or laboratory evidence of persistence or progression of infection, and at the time of any surgical or drainage procedure (if required).
Two sets of blood cultures were also collected at the screening visit (within 24 hours of enrollment) if the subject was febrile, if the subject had a urinary indwelling catheter or stent, or if a blood culture was otherwise clinically indicated. Subjects with identified bacteremia (positive blood cultures) had blood cultures collected daily until 2 consecutive cultures demonstrated no growth.

All urine and blood specimens were cultured and in vitro antimicrobial susceptibility testing, including susceptibility testing for carbapenems, was performed. All organisms considered to be etiologic pathogens by the investigator were sent to the central microbiology laboratory. Antimicrobial susceptibility testing was conducted using the CLSI reference BMD method.

The most commonly isolated pathogens overall were gram-negative aerobic bacilli (247 pathogens in 220 subjects), with *E. coli* being the most commonly isolated pathogen (159 pathogens in 143 subjects). Other common pathogens included *K. pneumoniae* (34 pathogens in 34 subjects) and *P. aeruginosa* (16 pathogens in 16 subjects). Additional details on pathogen distribution can be found in [Ref. 5.3.5.1: P003-05: Table 10-12]. The Applicant reported a total of 25 pathogens were not susceptible to imipenem, all of which were gram-negative aerobic bacilli. The most commonly isolated pathogen that was not susceptible to imipenem was *P. aeruginosa* (8 pathogens [32%]).

PN004 (cIAI)
At screening, samples from the site of infection were collected for culture (aerobic and anaerobic) and susceptibility testing. Cultures from the site of infection were obtained within 24 hours prior to trial entry for subjects enrolled intraoperatively or postoperatively. Subjects enrolled preoperatively were required to have cultures obtained within 24 hours following trial entry.

Two sets of blood cultures were also collected at the screening visit (within 24 hours of enrollment). Subjects with identified bacteremia (positive blood cultures) had blood cultures collected daily until 2 consecutive cultures demonstrated no growth. All intra-abdominal and blood specimens were cultured (aerobic and anaerobic) and in vitro antimicrobial susceptibility

testing, including susceptibility testing for carbapenems, was performed by the site's local laboratory. All organisms considered to be etiologic pathogens by the investigator were sent to the central microbiology laboratory. Antimicrobial susceptibility testing was conducted using the CLSI reference broth microdilution method.

The most commonly isolated pathogens overall were gram-negative aerobic bacilli (337 isolates in 223 subjects), with *E. coli* being the most common (171 pathogens in 165 subjects). Other common pathogens included *K. pneumoniae* (38 pathogens in 34 subjects) and *P. aeruginosa* (37 pathogens in 37 subjects). The Applicant reported that of the 40 isolates that were not susceptible (intermediate or resistant) to imipenem alone, there were 33 isolates (5.3% of the overall number of isolates) that were not susceptible to imipenem/REL. The most commonly isolated pathogen that was not susceptible to imipenem as well as to imipenem/REL was *P. mirabilis*.

Reviewer's Comment
The Applicant provided an explanation for the findings above as *P. mirabilis* is intrinsically less susceptible to imipenem by mechanisms independent of carbapenemase production.

Integrated analysis of PN002, PN003 and PN013 trials

Reviewer's Comment
This reviewer analyzed efficacy data by pathogen and by indication (cUTI and cIAI). The cUTI data was pooled from PN003 and PN013 and the cIAI data was pooled from PN004 and PN013. Likewise, any reliance on the imipenem-cilastatin labeling was done according to indicated pathogen. This is in contrast to some of the Applicant's analysis in which data was pooled across indications. The Agency's clinical and clinical microbiology team discussed the number of bacterial isolates in the PN003, PN004, and PN013 trials for each indication, and whether there were sufficient numbers for inclusion in the first list of organisms. For the indication of cUTI, there was insufficient number of clinical isolates of (b) (4) *K. aerogenes*, *E. cloacae* tested in imipenem-relebactam PN003 and PN013 clinical trials. Additionally, *C. freundii* is indicated for cIAI in the imipenem-cilastatin labeling. A sufficient number of clinical isolates were analyzed for *E. coli*, *K. pneumoniae*, and *P. aeruginosa*; however, the efficacy was 50% for *K. pneumoniae*. In addition to the clinical data here and the information from in vitro studies, the presence of these organism for the same indication in the imipenem-cilastatin labeling will provide support for their inclusion in the imipenem-relebactam labeling as well.

For the indication of cIAI, a sufficient number of clinical isolates was tested for *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. For the anaerobes, a sufficient number of *Bacteroides* was provided as a group.

Molecular Characterization of Bacterial Isolates from Clinical Studies
In the imipenem-relebactam clinical studies, isolates of Enterobacteriaceae and *P. aeruginosa* were characterized molecularly. For *P. aeruginosa,* a prominent beta-lactamase was PDC, an AmpC-type beta lactamase which has expanded spectrum activity toward imipenem due to mutations associated with the active site.

Reviewer's Comment
Relebactam has been described in the literature as having activity against PDC beta lactamases and its enzyme inactivation parameters for some PDC alleles have been described, particularly with respect to PDC-3. The KD is 23 +/- 3 nM for PDC-3[1]. One publication describes the most frequent AmpC variant as PDC-2 with G27D, A97V , T105A and V205L amino acid substitutions[1]. Although the Applicant provided evidence that relebactam can potentiate the activity of imipenem for *P. aeruginosa* isolates (e.g. against an expanded panel of *P. aeruginosa* that are not susceptible to imipenem) that produce PDC alleles, it is also important to note that there can be other resistance factors present that may be responsible for elevated imipenem MIC besides the presence of PDC beta lactamases and other beta lactamases.

There is a study report PD043MK7655-IHMA4374-MK7655 in which the Applicant describes porin gene analysis from selected isolates in the MK7655 clinical trial. Eighty-eight isolates including 55 *P. aeruginosa* were selected based on pre-established criteria for characterization. For *P. aeruginosa* the data is presented by subject ID, and information was provided on OprD (outer membrane porin) analysis, and beta-lactamase content. All of the *P. aeruginosa* isolates produced a PDC beta lactamase allele or plus up to three other identified beta lactamases including what is described as a new CTX-M variant. Other beta lactamases found in the isolates were from the following beta lactamase families: TEM, CTX-M, and VEB.

Reviewer's Comment

(b) (4)

[redacted]

[1] Barnes MD, Bethel CR, Alsop J, Becka SA, Rutter JD, Papp-Wallace KM, Bonomo RA. Inactivation of the Pseudomonas-Derived Cephalosporinase-3 (PDC-3) by Relebactam. Antimicrob Agents Chemother. 2018 Apr 26;62(5). pii: e02406-17. doi: 10.1128/AAC.02406-17. Print 2018 May.

15.6.6 Interpretive Criteria

Provisional Antimicrobial Susceptibility Testing (AST) Interpretive criteria
Imipenem breakpoints were used as provisional AST interpretive criteria for imipenem-relebactam.

Correlation of Broth MICs to Disk Zone Size
The performance of commercially manufactured imipenem-relebactam disks was evaluated by performing susceptibility testing on target pathogens by broth microdilution and disk diffusion using concurrent inocula at a reference testing laboratory. The Applicant used MIC and disk correlation studies to propose different disk zone diameter values for Enterobacteriaceae and *P. aeruginosa* from that of approved Imipenem-cilastatin label, although the MIC breakpoints for imipenem and those proposed for imipenem-relebactam by the Applicant are the same. See analysis below:

Reviewer's Comment
Data provided by the Applicant was displayed in scattergrams (not shown) with zone diameters on the x axis and MICs on the y axis. The error rate-bounded method was used to form a table with the total number of isolates tested and the number of minor, major, or very major discrepancies that were recorded for the isolates. The CLSI guidelines for acceptable discrepancy rates are below:

Table 112: CLSI Guideline for Acceptable Discrepancy Rates for MIC-Disk Correlation Studies

MIC Range	Very Major	Major	Minor
≥I+2	<2%	NA	<5%
I+1 to I-1	<10%	<10%	<40%
≤ I-2	NA	<2%	<5%

Source: Adapted from CLSI document M23-A4.

Reviewer's Comment
The aim of this analysis was to minimize discrepancy rates to best fit within CLSI guidelines. Minimizing error rates is important to prevent negative consequences for patients which could result from errors such as calling strains susceptible when they are known to be resistant. No scattergram analysis is shown for anaerobes as they use different methods for susceptibility testing (e.g. agar dilution rather than disk testing). The Applicant's proposals for disk diffusion have been accepted.

Susceptibility test interpretive criteria for imipenem-relebactam

The Applicant's proposed breakpoints for imipenem-relebactam are show in Table 113 below:

Table 113: Applicant's Proposed Interpretive Criteria for MIC Testing with Imipenem-Relebactam

Table 2.5: 2
Proposed Interpretive Criteria for Imipenem/Relebactam (CLSI)

Pathogen	Broth Microdilution MIC µg/mL			Disk Diffusion Zone Diameter (mm)			Agar Dilution MIC µg/mL		
	S	I	R	S	I	R	S	I	R
Enterobacteriaceae	≤1	2	≥4	≥25	21-24	≤20	NA	NA	NA
P. aeruginosa	≤2	4	≥8	≥23	20-22	≤19	NA	NA	NA
Anaerobes	NA	NA	NA	NA	NA	NA	≤4	8	≥16
A. baumannii	≤2	4	≥8	ND	ND	ND	NA	NA	NA

I = intermediate; MIC = minimum inhibitory concentration; NA = not applicable; ND = not determined, broth microdilution/disk correlation studies not conducted for *A. baumannii*; R = resistant; S = susceptible.

Source: [Ref. 5.4: 04ZX8X] [Ref. 5.3.5.4:PD048MK7655-IHMA3428]

Source: This submission.

Reviewer's Comment

The Applicant's proposal for MIC breakpoints for Enterobacteriaceae, *P. aeruginosa*, and anaerobes (agar dilution) matched the breakpoints accepted by FDA and by CLSI for imipenem, however, for Enterobacteriaceae and *P. aeruginosa*, the disk criteria were different. (b) (4) (b) (4) See clinical microbiology summary and recommendations for details. (b) (4) (b) (4)

The evidence of efficacy in the clinical trials and joint PTA assessment provide support to maintain existing imipenem broth microdilution breakpoints for IMI/REL. In addition, disk potency and broth microdilution correlation studies supported the use of 10/25 IMI/REL Kirby-Bauer disk for testing, which resulted in zone diameters that differentiate susceptible and resistant bacterial isolates.

The Applicant proposes to institute new breakpoints for Kirby-Bauer disk diffusion, employing a disk mass of 10 mcg imipenem and 25 mcg REL, based on analysis of the broth microdilution disk zone diameter correlation employing clinical and challenge isolates. The proposed disk mass of imipenem and relebactam is acceptable because it gave the best reproducibility.

Reviewer's Comment

The Agency's clinical pharmacology review team found their PK-PD target attainment analysis to be supportive of the breakpoints proposed by the Applicant for imipenem-relebactam. Additionally, the Agency's proposed breakpoints were most heavily based on the clinical microbiology in vitro data and reliance on the imipenem-cilastatin labeling as the clinical data

for the PN003, PN004 and PN013 trials was very limited. The favorable clinical responses shown by pathogen during imipenem-relebactam clinical trials are shown in the clinical section of the review.

15.6.7 Final Clinical Microbiology Recommendations

From a clinical microbiology perspective, the information provided by the Applicant supports the efficacy of imipenem relebactam for the treatment of susceptible bacteria for the indications of cUTI and cIAI. The following is a summary of the Agency's proposed clinical microbiology labeling changes and rationale:

- Subsection 12.4 has been updated in accordance with the FDA documents titled, "Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation: Guidance for Industry" and "Systemic Antibacterial and Antifungal Drugs: Susceptibility Test Interpretive Criteria Labeling for NDAs and ANDAs: Guidance for Industry".
- Quality Control ranges used for susceptibility testing have been accepted by the Clinical and Laboratory Standards Institute (CLSI) and are recommended here as published in the current CLSI document M100.
- (b) (4) Only well-supported and scientifically factual statements were recommended regarding these resistance factors.
- The first and second lists of organisms were edited according to relevance to the indication, and to meet the guidelines stated in the clinical microbiology guidance document. The following changes were recommended:
  (b) (4)
  - Gram-positive bacteria and anaerobes were included in the second list through reliance on approved IMI labeling and recent MIC data. (b) (4)
    (b) (4)

(b) (4)

- The Agency's breakpoint decisions for the organism groups listed below were based on the clinical microbiology in vitro data, PK/PD data, and support from the imipenem-cilastatin approval for the same pathogens for each indication.
- The Agency's proposed breakpoints are shown in the table below. The Applicant's proposal for breakpoints for Enterobacteriaceae, *P. aeruginosa* and anaerobes was accepted. (b) (4) (b) (4) (b) (4) It is recommended that a footnote be included to indicate which pathogens within the Enterobacteriaceae and anaerobes were tested. It is also recommended that the table reflect the use of 4 mcg/mL relebactam for MIC susceptibility testing as with other approved beta-lactam, beta-lactamase inhibitor combination products. As internal discussions within the Agency are ongoing, these may not represent the final breakpoints.

Table 114: Susceptibility Interpretive Criteria for Imipenem-Relebactam

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae [a]	≤1/4	2/4	≥4/4	≥25	21-24	≤20
Pseudomonas aeruginosa	≤2/4	4/4	≥8/4	≥23	20-22	≤19
Anaerobes [b,c]	≤4/4	8/4	≥16/4	-	-	-

S = Susceptible; I = Intermediate; R = Resistant

For disk diffusion, use paper disks impregnated with imipenem/relebactam at a concentration of 10/25 mcg/mL.

[a] *Klebsiella aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Klebsiella oxytoca.*

[b] *Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus, Bacteroides stercoris, Bacteroides thetaiotaomicron, Fusobacterium nucleatum, Parabacteroides distasonis.*

[c] Agar dilution method

Source: Reviewer's Table.

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/s/

CHRISTOPHER L SMITH
07/16/2019 04:42:46 PM

EDWARD M COX
07/16/2019 04:46:40 PM