CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209776Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number	NDA 209776
Priority or Standard	Priority
Submit Date	12/29/2016
Received Date	12/29/2016
PDUFA Goal Date	08/29/2017
Division/Office	DAIP/OAP
Reviewer Name	Rama Kapoor, M.D.
Established Name	Meropenem-vaborbactam
Proposed Trade Name	Vabomere (Proposed name)
Applicant	Rempex Pharmaceuticals a wholly owned subsidiary of The Medicines Company
Formulation	Powder for intravenous injection /meropenem 1000mg and vaborbactam 1000mg per vial
Dosing Regimen	4 g (meropenem 2 g-vaborbactam 2 g) every 8 hours by IV infusion over 3 hours.
Dosage Duration	(b) (4) 14 days
Applicant Proposed Indication/Population	Complicated urinary tract infections (cUTI), including pyelonephritis in patients 18 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	Complicated urinary tract infections (cUTI), including pyelonephritis in patients 18 years and older

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Glossary

AC	advisory committee
AE	adverse event
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
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 Harmonization
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
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
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
SIRS	Systemic Inflammatory Response Syndrome

1 Executive Summary

1.1. Product Introduction

Meropenem-vaborbactam is a fixed combination product constituted of an approved beta-lactam antibacterial drug meropenem (MERREM® approved in the US in 1996 under NDA 50,706), which belongs to a carbapenem class, and a cyclic boronic acid β-lactamase inhibitor vaborbactam. Vaborbactam is developed for inhibition of Class A serine carbapenemases, specifically the KPC enzyme. Vaborbactam lacks antimicrobial activity by itself; however, it restores activity of meropenem in the presence of bacterial beta-lactamases. Vaborbactam restores the activity of carbapenems against KPC-producing Carbapenem resistant Enterobacteriaceae (CRE) in vitro and in nonclinical models of infection.

Meropenem is an injectable carbapenem antibacterial drug that is FDA-approved for the treatment of complicated skin and skin structure infections (adults and pediatric patients), cIAI (adult and pediatric patients), and bacterial meningitis (pediatric patients)[1]. Meropenem is not approved for the treatment of complicated urinary tract infection (cUTI) in US; however it has been used for this indication in other parts of the world. Meropenem is considered to be efficacious, safe and well tolerated for the treatment of indicated infections. Meropenem has significant stability to hydrolysis by β-lactamases, both penicillinases and cephalosporinases, produced by gram-negative bacteria. Meropenem was approved in the US under the proprietary name of Merrem® IV and thereafter multiple generic versions are available. Meropenem trihydrate (b) (4) drug substance is synthesized by (b) (4) (b) (4) The DMF # (b) (4) is provided as a cross reference with this NDA.

Meropenem-vaborbactam clinical development program was aimed to address emerging resistance in gram-negative bacteria due to KPC-producing CRE.

The Applicant's proposed indication is treatment of patients with cUTI, including pyelonephritis.

The usual dosage regimen of meropenem-vaborbactam is 4 grams (meropenem 2 g and vaborbactam 2g) administered every 8 hours as a 3-hour infusion. The applicant has proposed a modified dosage regimen based on renal function.

The currently labeled indications for meropenem as described in the US package insert are summarized in Table below.

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050706s022lbl.pdf.

Indication	Pathogens
Complicated Skin and Skin Structure Infections (cSSSI)*	*Staphylococcus aureus (methicillin-susceptible isolates only), Streptococcus pyogenes, Streptococcus agalactiae, viridans group streptococci, Enterococcus faecalis (vancomycin-susceptible isolates only), Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis, and Peptostreptococcus species.*
Complicated Intra-abdominal Infections (cIAI)**	*Viridans group streptococci, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, B. thetaiotaomicron, and Peptostreptococcus species.*
Bacterial Meningitis***	*Haemophilus influenzae, Neisseria meningitidis* and penicillin-susceptible isolates of *Streptococcus pneumoniae*.
*(Adult Patients and Pediatric Patients 3 Months of Age and Older Only) **(Adult and Pediatric Patients) ***(Pediatric Patients 3 Months of Age and Older Only)	

1.2. Conclusions on the Substantial Evidence of Effectiveness

The reviewer recommends approval of meropenem-vaborbactam for the proposed indication. Data from an adequate, well controlled Phase 3 trial included in this application along with the known safety and efficacy profile of meropenem, provide substantial evidence of effectiveness as required by 21 CFR 314.126(a)(b) to support approval of meropenem-vaborbactam for the treatment of cUTI including pyelonephritis caused by, or suspected to be caused by, susceptible isolates of designated microorganisms. The regulatory endpoint of interest in this trial was overall success, which was a composite endpoint of clinical (Cure or Improvement) and microbiologic (Eradication or presumed Eradication) outcomes at end of intravenous treatment (EOIVT) in the microbiologic modified intent-to-treat (m-MITT) population. The non-inferiority was met for this endpoint. Overall success rates were higher in the meropenem-vaborbactam group compared to the comparator group.

The FDA guidance on developing antibacterial drugs for cUTI recommends that when a drug only has an intravenous formulation, the trial use co-primary endpoints at time points defined at the expected EOIVT and after expected completion of both intravenous and oral therapy (TOC visit). The reason to make both assessments is that the results at EOIVT visit are not affected by oral therapy, while sustained response following a period of observation after completion of treatment is considered more clinically meaningful. Study 505 only defined a single primary endpoint at the EOIV visit because the trial began before the FDA guidance was

finalized. At TOC visit, success rate in meropenem-vaborbactam treatment group was non inferior to piperacillin/tazobactam.

Therefore, the Applicant has provided sufficient evidence of the safety and efficacy of meropenem-vaborbactam to support its approval for the treatment of cUTI including pyelonephritis caused by meropenem susceptible pathogens.

1.3. Benefit-Risk Assessment Summary

Benefit-Risk Assessment Summary

Meropenem-vaborbactam is a fixed combination product of a β-lactam antibacterial from carbapenem class, meropenem ((MERREM® approved in the US in 1996 under NDA 50,706), and a cyclic boronic acid beta-lactamase inhibitor vaborbactam. Although lacking antimicrobial activity itself, vaborbactam restores the activity meropenem in the presence of beta-lactamases, by inhibition of bacterial beta-lactamases. The ability of vaborbactam to restore activity of carbapenems against KPC-producing Carbapenem resistant Enterobacteriaceae (CRE) is shown in vitro and in non-clinical studies. Data from an adequate well-controlled Phase 3 trial included in this application supports approval of meropenem-vaborbactam for the treatment of complicated urinary tract infections, including acute pyelonephritis caused by, or suspected to be caused by, meropenem susceptible isolates of designated microorganisms. The meropenem-vaborbactam combination product was designed to address the unmet need of the serious antimicrobial resistance threat due to KPC-producing CRE. Meropenem-vaborbactam fills an important unmet medical need in the treatment of cUTI and should be approved. This application provided statistical evidence that meropenem-vaborbactam is effective for the treatment of complicated urinary tract infections, including acute pyelonephritis and non-inferior to comparator, piperacillin/tazobactam.

Complicated urinary tract infections occur in patients with medical or surgical co-morbidities and are a public health concern. The bacterial spectrum of cUTIs is different from uncomplicated UTIs, which are primarily caused by *Escherichia coli* (83%). Although *E. coli* continues to be one of the most common etiologic agents of cUTIs, other pathogens such as *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Enterobacter spp*., *Proteus mirabilis*, *Serratia marcescens*, and *P. aeruginosa* are more common in the setting of cUTIs. Antimicrobial resistance is a concern for Gram-negative organisms because these comprise the dominant etiology of cUTIs. Treatment for cUTI primarily constitutes antibacterial therapy with coverage against Gram negative pathogens. The recommended treatment duration is up to 14 days depending on the response to treatment and presence of bacteremia.

There are a large number of antibacterial drugs that are available and FDA-approved for the treatment of cUTIs, including carbapenems such as imipenem/cilastin, doripenem, and ertapenem. Meropenem is not FDA approved for cUTI indication. Growing resistance in Gram negative pathogens to currently available treatment options is a serious threat and is recognized by CDC as an unmet need. The incidence of resistance to beta-lactam antibiotics in common UTI pathogens has been increasing mainly due to the spread of strains producing extended-spectrum beta-lactamases (ESBLs) such as CTX-M enzymes or Amp C beta-lactamases further limiting treatment options for cUTI. There is a specific unmet medical need for highly effective antibacterial treatments for cUTI. Meropenem generally maintains high potency against certain ESBL-producing strains. Carbapenem Resistant Enterobacteriaceae

(CRE) are bacteria that produces carbapenemases, such as *K. pneumoniae* carbapenemase (KPC). Vaborbactam has shown in vitro and non-clinical studies to potentiate the activity of meropenem against KPC producing CRE.

This application provided statistical evidence that meropenem-vaborbactam is effective for the treatment of complicated urinary tract infections, including pyelonephritis and non-inferior to the comparator, piperacillin/tazobactam. The efficacy of meropenem-vaborbactam is supported by a Phase 3 trial, Study 505. The primary efficacy endpoint in this trial was defined as Overall Response at the EOIV visit in m-MITT population. Overall Response was a composite endpoint requiring clinical cure or improvement, and also microbiological eradication (or in some cases presumed eradication). This was a noninferiority trial with a pre-specified margin of 15% on the risk difference scale. The rates of success for the Overall Response at EOIVT visit in the m-MITT analysis population were 189/192 (98.4%) for meropenem-vaborbactam and 171/182 (94.0%) for piperacillin/tazobactam group. The difference in success rates was 4.5%, and the lower confidence limit of 0.7% for the difference which exceeded zero. However, one of the drawbacks of this application is that an added role of the beta-lactamase inhibitor, vaborbactam was not supported by clinical data, as the majority of patients in the pivotal trial, Study 505 were infected with carbapenem susceptible pathogens.

This application also included interim results from an ongoing Phase 3 trial, Study 506.This study included patients with confirmed or suspected CRE infections including cUTI/AP, HABP/VABP, cIAI, or bacteremia (BSI). Patients in this trial had a greater level of underlying co-morbidities. However, interim clinical data from Study 506 are not sufficient to provide evidence of effectiveness of meropenem-vaborbactam compared to best available therapy in CRE infections.

The safety data for meropenem-vaborbactam was evaluated from the pivotal Phase 3 trial Study 505 and ongoing Study 506. Meropenem-vaborbactam demonstrated an overall favorable safety profile for the treatment of cUTI/ pyelonephritis. The rates and frequencies of AEs were similar to what is known to occur when meropenem is used for other approved indications. The most common TEAEs were headache, diarrhea, infusion-site phlebitis, and nausea. There were no new or major safety issues identified in this review. The safety issues with meropenem alone are well known and are not exacerbated by vaborbactam.

Overall, the patient population was comparable and balanced between two treatment arms in both Phase 3 trials. The range of underlying comorbidities in the safety population represents that encountered in clinical practice in U.S. with the exception of African Americans and other racial minorities and patients with moderate to severe renal insufficiency with CrCl<30ml/min, who were not well represented in these trials. While the biology of cUTIs and pharmacokinetics and pharmacodynamics of meropenem-

vaborbactam are not expected to significantly differ by race, a cautionary statement in the meropenem-vaborbactam label regarding the use of meropenem-vaborbactam in patients with moderate to severe renal insufficiency (with CrCl <30 ml/min) should be added. Applicant will also be advised to conduct a TQT study for this product as a PMR to exclude small QT prolongation effects (10 msec threshold). Other safety concerns associated with meropenem or meropenem-vaborbactam are adequately addressed in the product labeling.

1.3.1. Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Urinary tract infection is one of the most common bacterial infections in the general population, with an estimated overall incidence rate of 18 per 1000 person per year. UTIs account for more than 100,000 hospital admissions annually in the United States and are associated with significant morbidity and mortality as well as a high economic burden. Infection of urinary tract is also an important cause of sepsis in patients admitted to hospital and sepsis due to cUTI is associated with mortality of 20–40% in critically ill patients. • Complicated urinary tract infection (cUTI) is defined as UTI in a patient with a structural or functional abnormality due to intrinsic or extrinsic factors, and in patients with medical or surgical co-morbidities that predispose to persistent or relapsing infection. Acute pyelonephritis is a subset of cUTI which involves infection of kidneys and can occur in patients with or without functional or anatomic abnormalities of the urinary tract. • Complicated UTIs is diagnosed when a patient with underlying structural or functional abnormalities and other risk factors as mentioned above, presents with clinical features and laboratory evidence of a urinary	*Complicated urinary tract infection is a serious infection that occurs in patients with medical or surgical co-morbidities and is a public health concern.* *There are number of sequelae from cUTIs that may have serious or fatal consequences if left untreated or inadequately treated.* *It is an important cause of sepsis in patients admitted to hospitals. Sepsis due to*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infection. The clinical diagnostic criteria of cUTI include fever, worsened urinary urgency or frequency, acute dysuria, suprapubic tenderness, or costovertebral angle pain or tenderness. A positive urine culture commonly defined as $\geq 10^5$ CFU/mL with no more than two uropathogen and pyuria (10 white blood cells/high powered fields) are required to diagnose cUTI. Acute pyelonephritis presents with costovertebral angle pain or tenderness, often with fever, and variable lower tract symptoms. Some patients with neurological illnesses may be more difficult to assess because of atypical presentations. • The pathophysiology of cUTI is dependent on the interaction between the causative microorganism and the host. The bacterial spectrum of cUTIs is different from uncomplicated UTIs, which are primarily caused by *Escherichia coli* (83%). Although *E. coli* continues to be one of the most common etiologic agents of cUTIs, other pathogens such as *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Enterobacter spp.*, *Proteus mirabilis*, *Serratia marcescens*, and *P. aeruginosa* are more common in the setting of cUTIs. Antimicrobial resistance is a concern for Gram-negative organisms because these comprise the dominant etiology of cUTIs. • Administration of appropriate antibacterial therapy is the corner stone for cUTI treatment along with appropriate evaluation of severity of disease and underlying risk factors, and aggressive supportive care to reduce mortality. • Clinically significant outcomes include both microbiological eradication of the infecting pathogen and resolution of key signs and symptoms of cUTI (e.g., dysuria, urinary frequency, urinary urgency, flank pain, abdominal pain, suprapubic pain, costo-vertebral angle tenderness, fever and chills,	*cUTI may be associated with mortality of 20–40% in critically ill patients.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	nausea and vomiting). If cUTI is not appropriately treated it may have serious or fatal consequences. The most worrisome is sepsis, which is far more common with Gram-negative pathogens, and which may be fatal. It is more likely to occur in patients with underlying comorbidities such as diabetes, immunocompromised patients, those with chronic urological devices, or those with urinary obstruction. • There is an increasing antimicrobial resistance in Gram-negative pathogens. Production of β-lactamase enzymes by Gram-negative bacteria that hydrolyze the β-lactam ring results in decreased activity of beta-lactam antibiotics. Most uropathogens implicated in health-care-associated cUTIs, including catheter-related infections, are becoming resistant to multiple antimicrobial agents which is a serious public health concern.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Treatment for cUTI primarily constitutes antibacterial therapy with coverage against Gram negative pathogens. The hospitalized patients with cUTI are generally treated with beta-lactam antibiotics, cefepime or fluoroquinolones. The recommended treatment duration is up to 10 days, which can extend to 14 days if bacteremia is present. • There are a large number of antibacterial drugs that are available and FDA-approved for the treatment of cUTIs, including carbapenems such as imipenem/cilastin, doripenem, and ertapenem. Meropenem is not FDA approved for cUTI indication. • FDA acknowledges the importance of growing antimicrobial resistance among uropathogens and limited treatment options for cUTI caused by resistant pathogens. • Current therapies available to treat cUTI due to carbapenem-resistant Enterobacteriaceae include colistin, aminoglycosides and recently approved ceftazidime-avibactam.	*Approximately 80% of cUTIs is caused by Gram-negative pathogens. Growing resistance in Gram-negative pathogens to currently available treatment options is a serious threat and is recognized by CDC as an unmet need.* *Treatment options for cUTI are limited. There is a specific unmet medical need for highly effective antibacterial treatments for cUTI.*
Benefit	• This NDA for meropenem-vaborbactam (mer-vab) is accepted under Section 505(b) (2) of the FD&C Act. Evaluation of safety and efficacy of mer-vab partially relies on the FDA's previous findings of safety and effectiveness for meropenem, and data from a single, adequate and well-controlled Phase 3 trial, Study 505 for the cUTI/ pyelonephritis indication. • The primary efficacy endpoint in this trial was defined as Overall	*Meropenem-vaborbactam fills an important unmet medical need in the treatment of cUTI.* *This application provided statistical evidence that meropenem-vaborbactam*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Response at the EOIV visit in the microbiologic modified intent to treat population (m-MITT) population, which was defined as the randomized patients who received at least one dose of study drug and had a baseline bacterial pathogen(s) of $>10^5$ CFU/mL of urine in baseline urine culture or the same bacterial pathogen present in concurrent blood and urine cultures. Overall Response was a composite endpoint requiring clinical cure or improvement, and also microbiological eradication (or in some cases presumed eradication). This was a noninferiority trial with a pre-specified margin of 15% on the risk difference scale. • The rates of success for the Overall Response at EOIVT visit in the m-MITT analysis population were 189/192 (98.4%) for meropenem-vaborbactam and 171/182 (94.0%) for piperacillin/tazobactam (pip-tazo) group. The difference in success rates was 4.5%, and the lower confidence limit of 0.7% for the difference which exceeded zero. Study 505 provided statistical evidence that meropenem-vaborbactam is effective for the treatment of cUTIs, and is non-inferior to pip-tazo. • Despite the statistically significant difference between the two groups, overall success rates were high in both groups at this end point, which is not unexpected as patients in this trial were not critically ill and the majority of pathogens were sensitive to carbapenem. According to FDA guidance on cUTI, an IV investigational drug should demonstrate successful noninferiority (or superiority) at both, primary and co-primary endpoints. Co-primary efficacy endpoint is evaluated at a fixed time point after completion of the total duration of antibacterial therapy plus a period of 5-7 days	*is effective for the treatment of complicated urinary tract infections, including acute pyelonephritis and non-inferior to comparator, piperacillin/tazobactam.* *One of the drawbacks of this application is that, added role of betalactamase inhibitor, vaborbactam with meropenem was not demonstrated, as majority of patients (except 4 patients) in Study 505 were infected with carbapenem susceptible pathogens.* *Interim data from ongoing trial, Study 506 could not provide evidence of effectiveness in cUTI/* pyelonephritis *due to several limitations as mentioned.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	observation after completion of antibacterial drug therapy (which is TOC visit). Study 505 only defined a single primary endpoint at the EOIV visit because the trial began before the FDA guidance was finalized. • In Study 505, efficacy at TOC was evaluated as a secondary endpoint. Success rates at the TOC visit were lower in both treatment groups as compared to the EOIV visit; Overall Response of success at TOC was 74.5% for the mer-vab group and 70.3% for the pip-tazo group with a difference of 4.1%, and lower limit of confidence interval of -4.9, meeting non-inferiority criteria. There was similar proportion of failures in both treatment groups at TOC (21.4% in mer-vab and 22% in pip-tazo group), which were mainly due to recurrence of baseline pathogen. • Overall, demographic factors did not impact success rates in treatment groups. • This application also included interim results from an ongoing Phase 3 trial, Study 506 to provide supportive evidence for the cUTI/AP indication. This study included patients with confirmed or suspected carbapenem-resistant infections including cUTI/AP, HABP/VABP, cAI, or bacteremia (BSI). Patients in this trial had a greater level of underlying co-morbidities. • For subjects with cUTI or pyelonephritis at baseline, the primary efficacy endpoint was overall success at the TOC visit. Overall success required both microbiological eradication (baseline pathogens reduced to $<10^4$ CFU/mL or urine) and a Clinical Outcome of cure. In cUTI/ pyelonephritis patients, Overall success at TOC was (b) (4) for	*Although in-vitro data suggests effectiveness of mer-vab against certain beta-lactamases (especially KPC enzyme), clinical data (interim data from Study 506) is not sufficient to provide clinical evidence of effectiveness of mer-vab compared to best available therapy in CRE infections including cUTI.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mer-vab treatment group and [redacted] (b) (4) for BAT comparator treatment group in m-MITT population; and [redacted] (b) (4) and [redacted] (b) (4) in mer-vab and BAT comparator group in m-CRE-MITT population. • However, this trial was non-interpretable due to several limitations including interim nature of analysis of this ongoing trial, small sample size, and planned descriptive analysis. Therefore, Study 506 was not able to provide interpretable supportive evidence of efficacy for either cUTI/ pyelonephritis indication or for carbapenem-resistant Enterobacteriaceae infections. • Applicant proposes [redacted] (b) (4) The FDA guidance document on developing antibacterial drugs for cUTI recommends that when a drug only has an intravenous formulation and a trial has an option of oral switch, the trial use co-primary efficacy endpoints at approximately day 5 of IV therapy and at a fixed time point after randomization that accounts for the total duration of antibacterial therapy plus a period of observation after completion of antibacterial drug therapy. The reason to make both assessments is that the results at the EOIV visit are not affected by oral therapy, while sustained response after a period of observation after completion of treatment is considered more clinically meaningful. Study 505 only defined a single primary endpoint at the EOIV visit because the trial began before the FDA guidance was finalized. At TOC visit, success rate in the mer-vab	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	was non inferior to the pip-tazo group and both treatment groups had similar rates of failure due to recurrence of infection. Other limitations of Study 505 were as follows: - There was disproportionately higher number of 'indeterminate' outcomes in the comparator group; - Classification of outcomes were not reliably consistent and accurate at different study sites, in addition, there was a large number of key protocol violations especially in the mer-vab treatment group.	
Risk	• The analysis of safety of mer-vab in the treatment of cUTI/ pyelonephritis is based on known, favorable safety profile of meropenem for other approved indications, non-clinical data on safety of vaborbactam and clinical safety data from 337 patients exposed to proposed dose of mer-vab. There was no suggestion from this review that addition of vaborbactam induced or exacerbated the toxicity potential of meropenem. • TEAEs related to study drug and discontinuation of study drug due to TEAEs were slightly lower in the mer-vab treatment group compared to the comparator arms. The proportion of drug related TEAEs and all other TEAEs were similar in overall safety population. Life-threatening TEAEs were higher in the mer-vab group, whereas, severe TEAEs were higher in the comparator group. • The most frequently reported adverse reactions in patients receiving mer-vab in the Phase 3 clinical trials were headache, diarrhea, infusion site reactions, and hypersensitivity. The most common TEAEs	*Meropenem-vaborbactam demonstrated an overall favorable safety profile for the treatment of cUTI/* pyelonephritis. *There were no new or major safety issues identified in this review.* *The rates and frequencies of AEs were similar to what is known to occur when meropenem is used for other approved indications* *The most common TEAEs*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	were headache, diarrhea, infusion-site phlebitis, and nausea. Headache and infusion site inflammatory reactions were reported in a higher proportion of patients in the mer-vab group than in the comparator group. The rates and frequencies of AEs were similar to what is known to occur when meropenem is used for other approved indications. • Other than an 'infusion-related reaction' which led to study drug discontinuation in 2 (0.7%) patients in the mer-vab group and 0 patients in comparator group; and 'hypersensitivity' leading to discontinuations in 2 (0.7%) patients in each group in the Phase 3 trials, all other AEs leading to study drug discontinuation occurred in no more than 1 patient in either treatment group. Severe TEAEs occurred in 12 (4.1%) of patients in the mer-vab group and 19 (6.6%) of patients in the comparator group. Severe TEAEs reported for more than 1 patient included anemia (3 [1.0%] patients in each treatment group), seizure (0 patients in the mer-vab group and 2 [0.7%] patients in the comparator group), aspartate aminotransferase increased (1 [0.3%] in each treatment group), and colon cancer (1 [0.3%] in each treatment group). • There was no evidence of drug-induced liver injury or renal toxicity with meropenem-vaborbactam. • Vaborbactam also has no meaningful activity as an inducer or an inhibitor of CYP450 enzymes, and no activity as an inhibitor or substrate of drug transporters. • Overall, patient populations were comparable and balanced between two treatment arms in both Phase 3 trials. The range of underlying	*were headache, diarrhea, infusion-site phlebitis, and nausea.* *The safety issues with meropenem alone are well known and are not exacerbated by vaborbactam.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	comorbidities in the safety population represents that encountered in clinical practice in U.S. population with the exception of African Americans, and patients with moderate to severe renal insufficiency with CrCl<30ml/min, which were not well represented in this study. • There were no clinically relevant differences in vital signs between mer-vab and comparators. Overall, ECG data from Phase 1 and 3 studies with meropenem, vaborbactam, and the combination of the two, do not suggest that either drug has a clinically significant effect on ECG parameters, including the QTc interval.	
Risk Management	• Because the safety and efficacy of mer-vab in patients with moderate to severe renal insufficiency (with CrCl <30 ml/min) has not been studied in the Phase 3 trials, a study including these patients should be performed as PMR before mer-vab is used in this subgroup or a precautionary statement in the mer-vab label regarding use in this subgroup should be required. • The FDA Interdisciplinary Review Team for QT studies reviewed the cardiac safety report and recommended that the studies in current submission cannot be used to exclude small effects (10 msec) as per the ICH E14 and ICH E14 Q&A (R3) guidelines. Therefore, the Applicant should conduct a TQT study for this product as a PMR to exclude small QT prolongation effects (10 msec threshold). • Although no significant safety signals were detected in this review, the mer-vab prescribing information will include safety information contained in the current meropenem label, even if the events	*Applicant should conduct a TQT study for this product as a PMR to exclude small QT prolongation effects (10 msec threshold).* *Safety and efficacy of mer-vab in patients with moderate to severe renal insufficiency (with CrCl <30 ml/min) has not been studied in the Phase 3 trials, and therefore, a cautionary statement in the mer-vab label regarding use in this subgroup should*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	occurred rarely in the meropenem-vaborbactam trials: • Section 5 of the mer-vab label will include a warning regarding the risk of Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions • Although no cases of seizures were reported in the mer-vab group, warning regarding seizures and other adverse CNS experiences will be included in section 5 • Warnings regarding interaction with valproic acid will be included with instructions that antibacterial other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium.	*be provided.* *Other safety concerns associated with meropenem or meropenem-vaborbactam are adequately addressed in product labeling.*

2 Therapeutic Context

2.1. Analysis of Condition

The proposed indication for this application is complicated urinary tract infections (cUTI) including pyelonephritis.
A urinary tract infection (UTI) is an infection in the urinary tract, which runs from kidneys, through the ureters, the urinary bladder and out through the urethra. The current definitions of UTI are based on the 1992 IDSA[2] and 1993 ESCMID[3] guidelines. Uncomplicated urinary tract infection refers to infection in a structurally and neurologically normal urinary tract and typically affects individuals who are otherwise healthy. [4,5] Complicated UTIs are defined as UTIs associated with factors that compromise the urinary tract or host defense, including urinary obstruction, urinary retention caused by neurological disease, co-morbidities like diabetes mellitus, immunosuppression, renal failure, renal transplantation, pregnancy and the presence of foreign bodies such as calculi, indwelling catheters or other drainage devices or exposure to antibacterial drugs. [6,7] In addition, infection in men, pregnant women, children, and patients in health care–associated settings are considered complicated. In the patient with complicated infection, infecting microorganisms are more likely to be resistant to antimicrobial agents.

Pyelonephritis is a subset of cUTI that can occur in patients with or without functional or anatomic abnormalities of the urinary tract. Acute pyelonephritis is infection of the kidneys and generally requires initial parenteral antibacterial treatment and duration of therapy similar to other cUTIs.

The majority of UTIs are those acquired in the community setting (57.4%); 35.6% are healthcare-associated and 7% are nosocomial. Health care associated and nosocomial UTIs are almost always associated with instrumentation of urinary tract and thus are complicated in

[2] Rubin USE, Andriole VT, Davis RJ, Stamm WE. Evaluation of new anti-infective drugs for the treatment of UTI. Clin Infect Dis 1992; 15:216.
[3] Rubin UH SE, Andriole VT, Davis RJ, Stamm WE, with a modification by a European Working Party (Norrby SR). General guidelines for the evaluation of new anti-infective drugs for the treatment of urinary tract infection. The European Society of Clinical Microbiology and Infectious diseases, Taukirchen, Germany,
1993, p. 240–310.
[4] Hooton, T. M. Uncomplicated urinary tract infection. *New Engl. J. Med.* **366**, 1028–1037 (2012).
[5] Nielubowicz, G. R. & Mobley, H. L. Host–pathogen interactions in urinary tract infection. *Nature Rev. Urol.* **7**, 430–441 (2010).
[6] Lichtenberger, P. & Hooton, T. M. Complicated urinary tract infections. *Curr. Infect. Dis. Rep.* **10**, 499–504 (2008).
[7] Levison, M. E. & Kaye, D. Treatment of complicated urinary tract infections with an emphasis on drug-resistant Gram-negative uropathogens. *Curr. Infect. Dis. Rep.* **15**, 109–115 (2013).

nature.

The distinction between complicated and uncomplicated UTIs is vital because it has implications regarding the clinical evaluation, choice of empiric antibacterial therapy, consideration of surgical interventions (e.g., to relieve obstruction), and length of antibacterial therapy. The classification in complicated and uncomplicated UTI was intended to be a guide whether a UTI in a specific patient means an increased risk for a more serious outcome unless additional precautions or treatment modalities are applied. The bacterial spectrum of cUTIs is different from uncomplicated UTIs. Uncomplicated urinary tract infections are caused by a predictable group of susceptible organisms primarily *Escherichia coli* (83%) and can be successfully treated with a three-day course of oral antibacterial therapy. Although susceptible *E. coli* is responsible for more than 80% of uncomplicated UTIs, it accounts for less than one third of cUTI which is usually associated with resistant pathogens, need longer duration of therapy (10-14 days), and is associated with higher rate of recurrence and reinfections. Complicated UTIs are usually caused by a broader range of pathogens including *E.coli*, such as *Klebsiella pneumoniae*, *Enterobacter* spp., *Proteus mirabilis*, *Serratia marcescens*, *Enterococcus faecalis*, and *P. aeruginosa*, with an increase in relative frequency of non-*E. coli* pathogens.[8]

Complicated urinary tract infections can occur in both women and men, and in any age group. It is diagnosed when a patient with underlying structural or functional abnormalities and other risk factors as mentioned above, presents with clinical features and laboratory evidence of a urinary infection. In the absence of other causes, the clinical diagnostic criteria for cUTI include fever, worsened urinary urgency or frequency, acute dysuria, suprapubic tenderness, or costovertebral angle pain or tenderness. In addition, a positive urine culture ($\geq 10^5$ CFU/mL) with no more than two uropathogens and pyuria (10 white blood cells/high powered fields) is required to diagnose symptomatic UTI. Acute pyelonephritis presents with costovertebral angle pain or tenderness, often with fever, and variable lower tract symptoms. Some patients with neurological illnesses may be more difficult to assess because of atypical presentations. Patients with spinal cord injuries may present with symptoms such as increased bladder and leg spasms or autonomic dysreflexia, and patients with multiple sclerosis may experience increased fatigue and deterioration in neurological function. Clinical presentation of cUTI can vary, ranging from lower urinary tract symptoms (such as frequency and/or urgency) to systemic symptoms associated with bacteremia and sepsis. A positive urine culture in the absence of symptoms is called asymptomatic bacteriuria which is a significant bacteriuria, ≥100,000 cfu/mL on two successive urine cultures in an asymptomatic woman or from a single culture in asymptomatic men or from a catheterized urine specimen. Asymptomatic bacteriuria does not require treatment, except in pregnant women or those undergoing invasive genitourinary

[8] Wagenlehner FM, Pilatz A, Naber KG, Perletti G, Wagenlehner CM, Weidner W. Anti-infective treatment of bacterial urinary tract infections. Curr Med Chem 2008;15:1412-27.

procedures[9].
It is noteworthy that continued bacteriuria at greater than 10^4 CFU/mL represents a known risk for enhanced rate of relapse of cUTIs. Complicated UTIs are most often associated with recurrence of infection. Recurrences of UTI in patients who recently completed the treatment could be either relapse or reinfection. Relapse of bacteriuria refers to a recurrence of bacteriuria with the same infecting microorganism that was present before therapy was started. This is caused by the persistence of the organism in the urinary tract. Reinfection is a recurrence of bacteriuria with a microorganism different from the original infecting bacterium. It is a new infection. Reinfection may occur with the same microorganism, which may have persisted in the vagina or feces which can be mistaken for a relapse.

Urinary tract infections (UTIs) are one of the most common bacterial infections in the general population, with an estimated overall incidence rate of 18 per 1000 person per year.[10] Urinary tract infections account for more than 100,000 hospital admissions annually in the United States and are associated with significant morbidity and mortality as well as a high economic burden.[11] At least 40% of all hospital-acquired infections are UTIs. In the majority of cases, these infections are catheter-associated.[12] Furthermore, infection of urinary tract is also an important cause of sepsis in patients admitted to hospital.[13] Sepsis due to cUTI is associated with mortality of 20–40% in critically ill patients[14] and has a greater risk of morbidity and mortality.[15]

The natural history of untreated cUTI has not been consistently described. There are a number of sequelae from cUTIs if not properly treated that may have serious or fatal consequences.[16] These complications are more likely to occur in patients with underlying comorbidities such as diabetes, immunocompromised patients, those with chronic urological devices, or those with

[9] Nicolle, L. E. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin. Infect. Dis.* 40, 643–654 (2005).
[10] Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Community onset urinary tract infections: a population-based assessment. *Infection*. 2007;35(3):150–153.
[11] Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control. 2009;37(10):783–805.
[12] Wagenlehner FM, Naber KG. Treatment of bacterial urinary tract infections: presence and future. Eur Urol 2006;49(2):235-44.
[13] Levy MM, Artigas A, Phillips GS, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis 2012; 12: 919–24.
[14] Wagenlehner FM, Pilatz A, Naber KG, Weidner W. Therapeutic challenges of urosepsis. Eur J Clin Invest 2008; 38 (suppl 2): 45–49.
[15] Wagenlehner FM, Pilatz A, Naber KG, Weidner W. Therapeutic challenges of urosepsis. Eur J Clin Invest 2008; 38 (suppl 2): 45–49.
[16] D.E. Neal Jr. Host defense mechanisms in urinary tract infections. Infections in Urol ;Urol Clin North Am, 26 (4) (1999), pp. 677–686

urinary obstruction. [17,18]Sepsis due to cUTI is far more common with Gram-negative organisms, which are common cause of cUTIs, and it may be fatal. The hypotensive effects of the bacterial cell wall (endotoxin), coupled with a wide array of externally synthesized enzymes and other biologically active products, results in profound hemodynamic changes, multiple organ failure, and often death. Another ominous consequence of cUTIs is renal failure. This may be acute or chronic and may be permanent or self-limited. Pre-existing renal insufficiency by itself is a predisposing factor for cUTI (due to decreased renal blood flow), as is obstruction. One particular complication of cUTI is called emphysematous pyelonephritis, which occurs in diabetic patients. It is characterized by the finding of air in the renal parenchyma, identified by CT, ultrasound, or abdominal radiographs. Intervention is always required and even if instituted in a timely fashion, there is a high mortality rate. Other uncommon complications of cUTIs are xanthogranulomatous pyelonephritis and malakoplakia. Although uncommon, it almost always results in renal loss.

UTIs occur as a result of the interaction of bacterial virulence and host biologic and behavioral factors, superseding host defense mechanisms. With the exception of urethral mucosa, the normal urinary tract is resistant to colonization by bacteria and, for the most part, efficiently and rapidly eliminates pathogenic and nonpathogenic microorganisms that gain access to the bladder. Infection with a virulent organism by itself can make a UTI complicated even in otherwise normal urinary tract.

Treatment of cUTIs are increasingly becoming challenging due to growing antimicrobial resistance, especially among Gram-negative pathogens. [19] Most uropathogens implicated in health-care-associated cUTIs, including catheter-related infections, are resistant to multiple antimicrobial agents. [20,2122] As mentioned earlier, individuals with cUTIs frequently have recurrent infections, and thus they receive repeated courses of antimicrobial therapy. The SENTRY Antimicrobial Surveillance program indicates increased rates of resistance in

[17] Dembry LM, Andriole VT. Renal and perirenal abscesses. Infect Dis Clin North Am 1997;11:663-80.
[18] Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes. Infect Dis Clin North Am 1997;11:735-50.
[19] Sievert DM, Ricks P, Edwards JR, 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. *Infect Control Hosp Epidemiol*. 2013;34(1):1–14.
[20] Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-assciated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol 2013; 34: 1–14.
[21] Tandogdu Z, Cek M, Wagenlehner F, et al. Resistance patterns of nosocomial urinary tract infections in urology departments: 8-year results of the global prevalence of infections in urology study. World J Urol 2014; 32: 791–801.
[22] Wagenlehner FM, Cek M, Naber KG, Kiyota H, Bjerklund-Johansen TE. Epidemiology, treatment and prevention of healthcare-associated urinary tract infections. World J Urol 2012; 30: 59–67.

uropathogens globally. [23,24] Of particular concern are resistance in pathogens from Enterobacteriaceae family, as well as *Pseudomonas aeruginosa*. Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae (CRE), and multidrug-resistant (MDR) *P. aeruginosa* account for ~26,000, ~9,000, and ~6,700 health care-associated infections, respectively, in the USA each year.[25] Complicated UTI by itself is a risk factor for infection with antibiotic-resistant Gram-negative pathogen. Other risk factors for cUTIs caused by resistant pathogens include age older than 60 years, presence of a urinary catheter, chronic medical conditions, recent hospitalizations or antibiotic treatment, and recent travel. It is also noteworthy that the spectrum of pathogens implicated in cUTIs can vary according to geographic location, time period, and individual variability.

The primary goal of managing cUTIs is optimal administration of appropriate antimicrobial agents and correction of any underlying genitourinary abnormalities. This includes timely administration and appropriate selection and dosing of antimicrobial agents to which the potential pathogen is susceptible. Subsequently, delay in initiating the appropriate antimicrobial agent for severe cUTIs is associated with increased mortality.[26] Successful antimicrobial therapy will usually ameliorate symptoms with substantial clinical improvement in 48 h to 72 h. When the genitourinary abnormality predisposing to infection persists, a high frequency of recurrent infection is anticipated, usually at least 50% by six weeks post-therapy.[27,28] Resistance of the pre-therapy-infecting bacteria to the antimicrobial used for treatment is also associated with failure or relapse.[29] The variation of resistance rates of uropathogens varies widely among different regions, so continuous, regional surveillance on the microbial epidemiology is important for appropriate empiric antimicrobial selection.

A significant unmet medical need exists for effective, safe, and tolerable therapies for complicated UTIs caused by resistant pathogens. Draft guidance to industry on development of antibacterial therapies for patients with unmet medical need for the treatment of serious

[23] Peterson J, Kaul S, Khashab M, et al. Identification and pretherapy susceptibility of pathogens in patients with complicated urinary tract infection or acute pyelonephritis enrolled in a clinical study in the United States from November 2004 through April 2006. Clin Ther. 2007;29(10):2215–2221
[24] Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control. 2009;37(10):783–805.
[25] Hampton T. Report reveals scope of US antibiotic resistance threat. *JAMA*. 2013;310(16):1661–1663.
[26] Wagenlehner FM, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. *Clin Microbiol Infect*. 2006;12(suppl 3):67–80.
[27] Nicolle LE. A practical approach to the management of complicated urinary tract infection. Drugs and Aging 2001;18:243-54
[28] Nicolle LE, Mayhew JW, Bryan L. Outcome following antimicrobial therapy for asymptomatic bacteriuria in elderly women resident in an institution. Age Ageing 1988;17:187-92.
[29] Cox CE, Marbury TC, Pittman WG, et al. A randomized, double-blind multicenter comparison of gatifloxacin vs ciprofloxacin in the treatment of complicated urinary tract infection and pyelonephritis. Clin Ther 2002;24:223-36

bacterial diseases was released in July 2013[30] and guidance for drug development in complicated UTIs was released in February 2015[31], to facilitate drug development in these areas.

2.2. Analysis of Current Treatment Options

Antimicrobial treatment is a cornerstone in the treatment of cUTI. Without effective antibacterials the prognosis may be very serious. Treatment of cUTIs is based on patient tolerance, clinical presentation, prior antimicrobial use, urine culture reports, and local antimicrobial susceptibility patterns.[32] Initially an empiric antibacterial therapy for cUTI with broad spectrum activity should be started to cover the most commonly isolated pathogens, because it can take between 48 to 72 hours to obtain the results of culture and sensitivity of a urine specimen. Subsequently, delay in initiating the appropriate broad-spectrum antibacterial therapy for severe cUTIs is associated with increased mortality.[33] The empiric treatment should be followed by definitive treatment once the identity and susceptibilities of the causative organism are known. Some patients can be switched to oral antibacterial therapy after 3-5 days of successful intravenous treatment as long as they are clinically improving and able to tolerate the oral agent and a regimen is available that covers the identified pathogen(s).

Patients with cUTIs require up to 14 days of therapy. In pregnant patients, children and patients with recurrent pyelonephritis follow-up urine cultures should be performed within 10 to 14 days after treatment to ensure that the uropathogen has been eradicated. In clinical practice, in most non-pregnant adults follow-up cultures are not considered necessary, provided that the patient remains asymptomatic.

In clinical trials evaluating the efficacy of antibacterial drugs in cUTI, both microbiological eradication of the infecting pathogen and resolution of signs and symptoms of cUTI (e.g., dysuria, urinary frequency, urinary urgency, flank pain, abdominal pain, suprapubic pain, costo-vertebral angle tenderness, fever and chills, nausea and vomiting) are measured.

The hospitalized patients with cUTI are generally treated with beta-lactam antibacterial drugs or fluoroquinolones. The widespread use of fluoroquinolones has contributed to the rapid emergence of resistance over the past decade. Beta-lactam antibacterial drugs are among the

[30] https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm064980.htm
[31] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070981.pdf
[32] US Department of Health and Human Services. Food and Drug Administration: Draft Guidance for Industry. Complicated urinary tract infections - developing antimicrobial drugs for treatment. February 2012.
[33] Wagenlehner FM, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. *Clin Microbiol Infect*. 2006;12(suppl 3):67–80.

most commonly used classes of antibacterials to treat infections caused by Gram-negative bacteria. Treatment of cUTI has become difficult due to increasing antimicrobial resistance to beta-lactams and fluoroquinolones. [34,35] Production of β-lactamase enzymes by Gram-negative bacteria that hydrolyze the β-lactam ring results in decreased activity of beta-lactam antibiotics.

Beta-lactam antibacterial drugs are grouped together based upon a shared structural feature, the beta-lactam ring. Beta-lactam antibacterial drugs include penicillins, cephalosporins, cephamycins, carbapenems, and monobactams. Beta-lactam antibacterial drugs inhibit the growth of sensitive bacteria by inactivating enzymes located in the bacterial cell membrane. These enzymes can be detected by their covalent binding of radioactively-labeled penicillin (or other beta-lactams) and hence have been called penicillin binding proteins (PBPs).

There are three general mechanisms of bacterial resistance to beta-lactams: decreased penetration to or increased efflux from the target site; alteration of the target site; and inactivation of the antibacterial drug by a bacterial enzyme. Inactivation by a bacterial enzyme due to production of beta-lactamase is a major mechanism of resistance to the beta-lactam antibacterial drug in clinical isolates. Two classification schemes for β-lactamases are currently in use. The molecular classification is based on the amino acid sequence and divides β-lactamases into class A, C, and D enzymes which utilize serine for β-lactam hydrolysis and class B metallo-enzymes which require divalent zinc ions for substrate hydrolysis. The functional classification scheme takes into account substrate and inhibitor profiles in an attempt to group the enzymes in ways that can be correlated with their phenotype in clinical isolates. Major groupings generally correlate with the more broadly based molecular classification. This includes group 1 (class C) cephalosporinases; group 2 (classes A and D) broad-spectrum, inhibitor-resistant, and extended-spectrum β-lactamases and serine carbapenemases; and group 3 metallo-β-lactamases. Class A enzymes include narrow-spectrumβ-lactamases (produced by *Escherichia coli*, *Klebsiella pneumoniae*), ESBLs (produced by Enterobacteriaceae, *Pseudomonas aeruginosa*), and carbapenemases (produced by *K. pneumoniae*).

Except for the carbapenemases, β-lactamases are generally inhibited in vitro by the β-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam. Class B enzymes are generally carbapenemases and are not inhibited by the available β-lactamase inhibitors. Class C enzymes are often chromosomally mediated, inducible cephalosporinases such as AmpCs, which are usually produced by the organisms in the "SPACE" genera (*Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter*, and *Enterobacter*). Class D enzymes are usually extended-spectrum

[34] Hoban DJ, Bouchillon SK, Hawser SP, Badal RE. Trends in the frequency of multiple drug-resistant Enterobacteriaceae and their susceptibility to ertapenem, imipenem, and other antimicrobial agents: data from the Study for Monitoring Antimicrobial Resistance Trends 2002 to 2007. *Diagn Microbiol Infect Dis*. 2010;66:78–86.

[35] Alhambra A, Cuadros JA, Cacho J, et al. In vitro susceptibility of recent antibiotic-resistant urinary pathogens to ertapenem and 12 other antibiotics. *J Antimicrob Chemother*. 2004;53:1090–1094.

beta-lactamases (ESBLs) and carbapenemases. [36,37]

The incidence of resistance to beta-lactam antibiotics in common UTI pathogens has been increasing mainly due to the spread of strains producing ESBLs. In the US, 6.8% of *E. coli*, 10.3% of *Klebsiella pneumoniae*, 3.7% of *Proteus mirabilis*, and 11.1% of *Klebsiella oxytoca* isolates are reported to produce ESBLs.[38] Meropenem generally maintains activity against ESBL-producing strains. There is a recent emergence of carbapenem-resistant Enterobacteriaceae (CRE), which produces carbapenemases such as, *K. pneumoniae* carbapenemase (KPC), Verona integron-encoded metallo-β-lactamase (VIM), New Delhi metallo-β-lactamase (NDM), and oxacillin-hydrolyzing (OXA)-48 types, and neutralizes carbapenems in addition to penicillins and cephalosporins further limiting treatment options.[39] *K. pneumoniae* carbapenemase (KPC) are the most common in the US. [40] These enzymes are encountered in Enterobacteriaceae species, particularly *K. pneumonia* and *E. coli*, and less frequently in other Gram-negative organisms such as *P. aeruginosa*, *Acinetobacter baumanii*, and *S. marcescens*. In a recent population- and laboratory-based active surveillance study, the incidence of CRE was 2.93 per 100,000 populations in the US where most CRE cases were isolated from a urinary source, and were associated with high prevalence of prior hospitalizations or indwelling devices, and discharge to long-term care settings.[41] The rate of CRE infections varies from region to region, and it is estimated to be 1.8–2.4% based on the US, European, and Latin American data as reported in the SENTRY study.[42]

Table 1 below provides a brief synopsis of antibacterial products currently FDA approved for the treatment of cUTI.

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[36] Toussaint KA, Gallagher JC. Beta-lactam/beta-lactamase inhibitor combinations: from then to now. Ann Pharmacother. 2015;49(1):86–98.

[37] Liscio JL, Mahoney MV, Hirsch EB. Ceftolozane/tazobactam and ceftazidime/avibactam: two novel beta-lactam/beta-lactamase inhibitor combination agents for the treatment of resistant Gram-negative bacterial infections. Int J Antimicrob Agents. 2015;46(3):266–271.

[38] Bouchillon SK, Badal RE, Hoban DJ, Hawser SP. Antimicrobial susceptibility of inpatient urinary tract isolates of gram-negative bacilli in the United States: results from the study for monitoring antimicrobial resistance trends (SMART) program: 2009-2011. Clin Ther. 2013;35(6):872-7.

[39] Cantón R, Akóva M, Carmeli Y, et al. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect. 2012;18(5):413–431.

[40] Jacob JT, Klein E, Laxminarayan R, et al. Vital signs: carbapenem-resistant Enterobacteriaceae. MMWR Morb Mortal Wkly Rep. 2013;62:165–170.

[41] Guh AY, Bulens SN, Mu Y, et al. Epidemiology of carbapenem-resistant Enterobacteriaceae in 7 US communities, 2012-2013. JAMA. 2015;314(14):1479–1487

[42] Castanheira M, Mendes RE, Woosley LN, et al. Trends in carbapenemase-producing Escherichia coli and Klebsiella spp. from Europe and the Americas: report from the SENTRY antimicrobial surveillance programme (2007–09). J Antimicrob Chemother. 2011;66:1409–1411.

Table 1 Summary of Currently Approved Treatment for cUTI

Generic name	**Trade name**	***Comments***
Extended-spectrum penicillins		
Piperacillin	Piperacil	*cUTI caused by susceptible strains of Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii or Klebsiella pneumoniae.* **Ceftazidime also active against Pseudomonas aeruginosa;* *Use as an empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli*
Cephalosporins : Parenteral 2nd 3rd and 4th generation		
Cefotetan	Caftan	
Cefotetan	Metoxen	
Cefuroxime sodium	Zinacef	
Cefotaxime	Claforan	
Ceftazidime	Fortaz, Tazice	
Ceftriaxone	Rocephin	
Cefepime	Maxipime	
Fluoroquinolones		*cUTI caused by Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, or Pseudomonas aeruginosa.* **Safety risks including tendonitis, tendon rupture, QT c prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy*
Levofloxacin	Levaquin	
Ciprofloxacin	Cipro	
Carbapenems		
Imipenem-cilastatin	Primaxin	*cUTI caused by susceptible strains of Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains) , Enterobacter species, Escherichia coli, Klebsiella species, Morganella morganii , Proteus vulgaris , Providencia rettgeri , Pseudomonas aeruginosa*
Ertapenem	Envanz	
Doripenem	Doribax	
Monobactams		*Infections caused by Caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca, Citrobacter species, and Serratia marcescens.* **Although used in pts with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime*
Aztreonam	Azactam	
Aminoglycosides		
Gentamicin		*Indicated in the <u>short-term treatment</u> of serious infections due to susceptible strains of Gram-negative bacteria, including Pseudomonas species, Escherichia coli, species of indole-positive and indole-negative Proteus, Providencia species, Klebsiella-Enterobacter-Serratia species, and Acinetobacter species.* ** Safety risks including nephrotoxicity, neurotoxicity and ototoxicity.*
Amikacin		
Tobramycin		
Tetracyclines		*Indicated for the treatment of infections caused by*

Generic name	Trade name	*Comments*
Minocycline	Minocin	*susceptible strains of Escherichia coli, Enterobacter aerogenes, Shigella species, Acinetobacter species, and Klebsiella species.* ** Safety risks including hepatic and renal toxicity*
Polymyxins		
Polymyxins	Poly-Rx	*Some gram-negatives are intrinsically resistant (e.g. Proteus* spp. *Providencia* spp. Serratia spp., *B. cepacia*), **Safety risks including nephrotoxicity and rare but serious neurotoxicity*
Colistimethate	Coly-mycin M	
Sulfa		
Trimethoprim-Sulfamethoxazole	Bactrim	*Usually not used for complicated UTI*
β-lactam/β-lactamase Inhibitor Combinations		Described in more detail in Table 2.
Ticarcillin clavulanate	Timentin	Currently discontinued in the US
Ceftolozane-tazobactam	Zerbaxa	
Ceftazidime-avibactam	Avycaz	
Note: Beta-lactam antibiotics are grouped together based upon a shared structural feature, the beta-lactam ring. There are several classes of beta lactam drugs e.g. Penicillins, Cephalosporins, Cephamycins, Carbapenems, Monobactams.		

Table below displays a list of currently approved beta lactam (BL) drugs and beta-lactamase inhibitor (BLI) combinations. All BL-BLI combinations are primarily excreted through the kidneys and require dosage adjustment in patients with impaired renal function.

Table 2 Currently Approved β-lactam/β-lactamase Inhibitor Combinations

Generic name	Trade name	Year of	Comment
Ticarcillin-clavulanate	Timentin	1985	Currently discontinued in the US
Ampicillin-sulbactam	Unasyn	1986	Not approved for cUTI
Piperacillin-tazobactam	Zosyn	1993	Not approved for cUTI
New β-lactam–β-lactamase inhibitor combinations			
Ceftolozane-tazobactam	Zerbaxa	2014	Indicated for the treatment of cUTI, including pyelonephritis, caused by the following Gram-negative microorganisms: *Escherichia coli*, *Klebsiella, pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

Ceftazidime-avibactam	Avycaz	2015	Indicated for the treatment of cUTI including pyelonephritis caused by the following susceptible Gram-negative microorganisms: *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Citrobacter freundii* complex, *Proteus mirabilis,* and *Pseudomonas aeruginosa.*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This is a first marketing application for meropenem-vaborbactam fixed drug combination product. The combination is currently not marketed in the U.S. or anywhere in the world.

Meropenem-vaborbactam is a combination of meropenem, a carbapenem antibacterial drug that had been marketed in U.S. and worldwide for over 2 decades and a beta- lactamase inhibitor vaborbactam (formerly called RPX7009), a novel molecular entity, which restores the activity of carbapenems against KPC-producing CRE in vitro and in nonclinical models of infection has not been marketed in the US or anywhere in the world.

3.2. Summary of Presubmission/Submission Regulatory Activity

This section will summarize and focus only on the notable events which directly impacted the current NDA.

An initial investigational new drug application (IND) for meropenem/RPX7009 was submitted on December 23, 2013 by Rempex Pharmaceuticals, Inc. After a 30-day safety review, it was determined the Sponsor may proceed with the proposed clinical investigation under IND 120040 on February 6, 2014. Notably, in the pre-IND stage, on December 19, 2013, meropenem-vaborbactam was granted a QIDP designation for febrile neutropenia, cUTI, IAI, HABP, and VABP.

Clinical protocols and the development plan were reviewed by the Division throughout the meropenem/vaborbactam development program, with feedback provided regarding issues of dose selection, treatment duration, treatment regimen, and trial population.

An End of Phase 2 meeting was held on March 28, 2014 to discuss the meropenem vaborbactam Phase 3 development program and the proposed registration plan. FDA provided feedback on the design of Phase 3 Studies, Studies 505 and 506. The protocol designs later

submitted to the Division were determined to be acceptable.

An End of Phase 2 CMC meeting was held on July 3, 2014. During this meeting, the starting materials and the control strategies for impurities and stereochemistry and design of the microbial challenge study were discussed. FDA provided feedback on the drug substance and drug product testing programs.

A type-B meeting was held on March 2, 2015 to discuss pediatric development program and the proposed Pediatric Study Plan. Proposed Pediatric Study Plan was accepted by FDA on December 2, 2015.

On September 30, 2015, a meeting was held to discuss Phase 3 studies, NDA filing plans, CMC development program. One agreement resulting from this meeting was an acceptability of widening the NI margin to 15% in Study 505 and agreement on the size of the preapproval safety database to be provided in the NDA (approximately 300 subjects treated with the proposed dose and treatment duration for meropenem-vaborbactam). The applicant also requested waiver for thorough QT studies. FDA QT Interdisciplinary Review Team recommended a thorough QT study noting that previous preclinical information and cardiovascular safety assessment in clinical trials are not sufficient to rule out small increases in the QTc interval (<10 ms). The thorough QT study could be conducted as a post-marketing requirement (PMR).

Fast Track designation was granted for meropenem-vaborbactam on March 21, 2016.

A pre-NDA meeting was held on November 3, 2016. The purpose of this meeting was to discuss the FDA feedback on the high-level safety and efficacy results from the completed Phase 3 study, Study 505, and from an interim analysis using a data cut-off date of 31 March 2016 from the ongoing, supportive, Phase 3 study, Study 506.

The FDA noted that one review issue in assessing the statistically significant difference found in Study 505 between meropenem-vaborbactam and piperacillin-tazobactam for the primary analysis may be to further analyze subjects with missing or indeterminate clinical or microbiological outcomes.

During this meeting, FDA also informed the Sponsor that all of the available nonclinical study information for the two compounds whether derived from new studies conducted for the IND, information from the Merrem product label or derived from the literature should be included in the NDA submission.

The Sponsor referred to a previous written communication from the FDA dating from a March 28, 2014 meeting with the Sponsor where the following recommendation from the FDA was submitted: “A pre-postnatal study for meropenem is recommended. Alternatively, the addition of a meropenem treatment group in the pre-postnatal study planned for RPX7009 may be acceptable.” With reference to this previous recommendation, the Sponsor asked if the pre-

postnatal study with meropenem was still necessary in light of new clinical postnatal data for meropenem and new juvenile toxicity data for meropenem. The FDA replied that a nonclinical pre-postnatal study for meropenem was still necessary. In response, the Sponsor asked if pre-postnatal information described in a publically available Merrem Product Monograph by AstraZeneca Canada Inc. would provide sufficient information. The FDA replied that it might, but a final determination would be a review decision dependent on the depth of information included the monograph. Upon reviewing the pre-postnatal study information in the Product Monograph for Merrem by AstraZeneca Canada Inc., FDA suggested that the summary information included in the monograph is not sufficiently comprehensive to allow review and evaluation. In order to be included in the product label, nonclinical study information must be sufficiently comprehensive to allow review. FDA recommended the sponsor to obtain either right of reference from AstraZeneca for the meropenem pre-postnatal study and submit the complete study report for review, or conduct a nonclinical pre-postnatal study with meropenem.

An agreement was made between FDA and sponsor that the NDA for meropenem-vaborbactam could be filed under the 505(b) (2) pathway. Rempex agreed to include the requested meropenem drug substance information in the NDA, in addition to the DMF, as an aid to the reviewer. It was also agreed that additional stability data could be submitted as a minor application component within 4 months after the submission of the original application. Agreements and guidance on studies to be referenced under 505(b) (2) pathway was provided.

The details of the milestone meetings can be found in the official meeting minutes archived in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). All previous reviews can also be accessed in DARRTS for additional information.

The NDA was submitted on December 29, 2016.

3.3. Foreign Regulatory Actions and Marketing History

At the time this review was finalized, meropenem-vaborbactam or vaborbactam alone have not been marketed in any country.

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

4.1. Office of Scientific Investigations (OSI)

Three sites from Ukraine (site ID 804-005, 804-002, and 804-009)), and one site from Greece (site ID 300-001) were selected for inspection based on OSI Inspections risk assessment tool and clinical reviewers' review of CRFs.

Reviewer Comment: At the time of completion of this review, the results of the site inspections are still pending.

4.2. Product Quality

Meropenem trihydrate [redacted] drug substance is synthesized by [redacted] [redacted] holds an active Drug Master File (DMF) No. [redacted] on [redacted] meropenem trihydrate. The chemical name for meropenem is (4R, 5S, 6S)-3- [[(3S, 5S)-5-(Dimethyl carbamoyl)-3-pyrrolidinyl] thiol]-6- [(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclic [3.2.0] hept-2-ene-2-carboxylic acid trihydrate.

Vaborbactam [redacted] is synthesized at [redacted] The chemical name for vaborbactam is (3R, 6S)-2-hydroxy-3-[[2-(2-thienyl) acetyl] amino]-1, 2-oxaborinane-6-acetic acid.

Meropenem-vaborbactam for Injection drug product is a powder [redacted] of [redacted] meropenem trihydrate, [redacted] vaborbactam, and [redacted] sodium carbonate containing 1000 mg each of meropenem and vaborbactam per vial in a 50 mL USP Type I glass vial capped with a [redacted] rubber stopper and flip-off aluminum seal. Meropenem-vaborbactam for Injection drug product is intended for intravenous administration after reconstitution and further dilution with 0.9% sodium chloride injection USP prior to use.

Meropenem-vaborbactam for Injection is manufactured in accordance with current Good Manufacturing Practices (cGMP) by [redacted] using standard processing techniques.

Please refer to review by the FDA Product Quality reviewer for further details.

4.3. Clinical Microbiology

The clinical microbiological results are presented in Section 6. In this section, a summary of microbiological activity from preclinical studies is presented. Reader is referred to the review by FDA microbiology reviewer, Kerian Grande Roche, Ph.D. for details of microbiology information. The information presented below is obtained from the Applicants' submission.

Mechanism of Action

Meropenem is a broad-spectrum, injectable, carbapenem antibacterial drug, which Inhibits bacterial cell-wall synthesis by binding to penicillin-binding proteins. Vaborbactam is a novel cyclic boronic acid beta-lactamase inhibitor that is developed for inhibition of Class A serine carbapenemases, primarily KPC enzymes which are produced by gram negative bacteria.

Although lacking antimicrobial activity itself, vaborbactam restores the activity of concomitantly administered meropenem, by inhibition of bacterial beta-lactamase. The contribution of vaborbactam to meropenem-vaborbactam is based on data from in vitro studies and animal models of infection.

The kinetics of vaborbactam inhibition of KPC-2 is consistent with covalent inhibition and progressive enzyme inactivation. Vaborbactam was also shown to be a reversible inhibitor of KPC-2 with a very slow "off-rate", resulting in an enzyme residency time lasting multiple hours. Based on stoichiometric analysis, only one molecule of vaborbactam is required to inactivate one molecule of KPC-2 enzyme compared to >64 molecules of either tazobactam or clavulanic acid. Site-directed mutagenesis studies demonstrated that the inhibition potency of vaborbactam against KPC is unaffected by KPC mutations that have been shown to reduce the KPC inhibition potency of other beta-lactam inhibitors, including avibactam.

In Vitro Susceptibility

The in vitro activity of meropenem alone and in combination with vaborbactam at a fixed concentration was evaluated against KPC-producing strains of Enterobacteriaceae in several prospective and retrospective surveillance studies that included the evaluation of over 1,900 isolates, including 619 from the US. Many of these strains produced other extended spectrum beta-lactamase enzymes in addition to KPC.

Vaborbactam, at a fixed concentration of 8 µg/mL, significantly enhanced the activity of meropenem against KPC-producing strains with the lowest concentration of meropenem at which 90% of the isolates were inhibited (MIC90) ranging from 0.5 µg/mL to 2 µg/mL for meropenem-vaborbactam versus >32 µg/mL for meropenem alone.

Vaborbactam was also evaluated for any intrinsic antimicrobial activity by incubation with selected strains of Enterobacteriaceae, *Acinetobacter baumanii*, and *Pseudomonas aeruginosa* (*P. aeruginosa*). The minimum inhibitory concentrations (MICs) for vaborbactam were greater than 32 µg/mL in all strains tested, supporting a lack of intrinsic antimicrobial activity.

Potential for Resistance Development

An in vitro hollow fiber pharmacodynamic (PD) model was used to evaluate the effects of meropenem and vaborbactam in combination against 11 clinical isolates of *K. pneumoniae*, 3 clinical isolates of *E. cloacae*, 3 isolates of *P. aeruginosa*, and 1 isolate of *E. coli*. A dosage regimen of meropenem 2 g-vaborbactam 2 g was highly effective against *K. pneumoniae*, *E. cloacae*, and *E. coli* strains with potentiated meropenem MICs of up to 8 µg/mL (tested with a fixed 8 µg/mL vaborbactam). This dosage regimen produced over 4 logs of bacterial killing against all strains tested and suppressed the development of resistance. A single isolate with a potentiated meropenem MIC of 16 µg/mL (tested with a fixed 8 µg/mL vaborbactam) appeared

to be responding to treatment over 16 hours, but the experiment was ended at that time due to regrowth of two other isolates with potentiated meropenem MICs of 32 µg/mL or higher (tested with a fixed 8 µg/mL vaborbactam). These data show that the intended clinical dosage regimen of meropenem 2 g vaborbactam 2 g administered by a 3-hour infusion q8h results in bactericidal activity and suppression of resistance in Enterobacteriaceae with meropenem MICs ≤8 µg/mL (when tested with a fixed concentration of 8 µg/mL of vaborbactam).

For *P. aeruginosa*, meropenem 2 g in combination with vaborbactam 2 g q8h by 3-hour infusion was effective against all three strains of *P. aeruginosa* tested, producing over 4 logs of bacterial killing and suppressing the development of resistance. No significant changes in MICs were observed for either meropenem or meropenem-vaborbactam in Studies 505 and 506.

Susceptibility Testing and Breakpoints

The Applicant has proposed MIC breakpoints for meropenem-vaborbactam (all tested with a fixed vaborbactam concentration of 8 µg/mL). MIC breakpoints for meropenem-vaborbactam susceptibility were developed based on non-clinical PK-PD, MIC distributions, and clinical results. Meropenem-vaborbactam MIC testing in the presence of a fixed concentration of 8 µg/mL of vaborbactam was supported by the following observations:

i. Vaborbactam 8 µg/mL was associated with >90% of the maximal proportion of KPC-producing isolates inhibited by meropenem 8 µg/mL;
ii. Average free plasma vaborbactam concentrations over 24 hours in humans following 2 g doses q8h exceed 8 µg/mL, indicating that the selection of 8 µg/mL as the vaborbactam testing concentration is relevant in vivo;
iii. MIC testing of meropenem with 8 µg/mL of vaborbactam correlated best with in vivo results in a mouse model of infection;
iv. Mathematical PK-PD modeling in the hollow fiber model developed a significant relationship between vaborbactam exposure and effect based on MIC testing of meropenem in combination with 8 µg/mL of vaborbactam.

Based on the data above, susceptibility test development focused on meropenem MIC testing in the presence of a fixed 8 µg/mL of vaborbactam.

Surveillance studies indicated that over 90% of KPC-producing CRE are inhibited by ≤8 µg/mL meropenem (with a fixed 8 µg/mL of vaborbactam).
PK-PD data in animal and in vitro models of infection using simulated human plasma PK for meropenem 2 g-vaborbactam 2 g infused over 3 hours q8h showed bactericidal effects and no emergence of resistance in KPC-producing CRE with meropenem MICs ≤8 µg/mL (with a fixed 8 µg/mL of vaborbactam).

A Monte Carlo PK-PD simulation of meropenem and vaborbactam plasma concentrations using the proposed dosage regimen in 4,000 patients was conducted using four creatinine clearance groups (1,000 patients per group): 40-150 mL/minute; 20-39 mL/minute; 10-20 mL/minute; and <10 mL/minute.
PK-PD exposure targets from nonclinical models for meropenem and vaborbactam in Enterobacteriaceae (including KPC-producing strains) and *P. aeruginosa* were obtained in >90% of simulated patients overall and in each of the creatinine clearance groups for meropenem MICs ≤8 µg/mL (with a fixed 8 µg/mL of vaborbactam).

Table below presents the MIC breakpoints for meropenem-vaborbactam as proposed by the Applicant:

Table 3 MIC Breakpoints for meropenem-vaborbactam

(b) (4)

Reviewer Comment: The discussion of the breakpoints continued at the time this review was written.

4.4. Nonclinical Pharmacology/Toxicology

The Applicant seeks to support registration of meropenem-vaborbactam treatment regimens of up to two weeks in duration on the basis of the repeat dose toxicity studies, which were conducted either with vaborbactam alone or in combination with meropenem for up to 28 days, with 28 days recovery.

The toxicity profile of meropenem is well established. The toxicity profile of vaborbactam was examined in single dose, repeat dose, genotoxicity, reproductive and developmental toxicity studies, and studies in juvenile animals. Studies were conducted with vaborbactam alone or in combination with meropenem. Except for range-finding studies, these studies were conducted in compliance with Good Laboratory Practice regulations (GLPs).

Vaborbactam (RPX7009) was not associated with significant toxicities in 28-day repeated-dose toxicology studies in rats and dogs at daily doses as high as 1000 mg/kg/day (respectively approximately equal to or 3 times the maximum recommended human dose in patients based on plasma AUC exposure) when administered alone or in combination with meropenem. A similar lack of toxicity occurred in a 28-day toxicology study in juvenile rats with the same NOAEL of 1000 mg/kg/day. Vaborbactam was not associated with genotoxicity in a full battery of testing (*in vitro* Ames test, chromosome aberration test in human lymphocytes and *in vivo*

micronucleus test in mice). In reproductive and developmental toxicology studies, vaborbactam at a dose of 1000 mg/kg/day in all studies did not negatively affect male or female fertility or embryonic development in pregnant rats and rabbits and had no effects on first or second generation offspring in rats in a pre-postnatal study. In rats and rabbits respectively, the NOAEL dose of 1000 mg/kg/day was approximately equal to or 5-times the maximum recommended human dose in patients based on plasma AUC exposure.

In combination toxicology studies in rats and dogs meropenem did not produce significant toxicities, and the NOAEL for each study was the dose of 500 mg/kg/day when administered alone or in combination with vaborbactam for 28 days. Meropenem was not genotoxic in a full battery of *in vitro* (Ames test, Chinese hamster ovary HGPRT assay, human lymphocyte cytogenic assay) and *in vivo* (mouse micronucleus assay) assays. In fertility studies in rats with a dose of 1000 mg/kg/day (approximately equal to the highest recommended human dose in patients based on plasma AUC exposure) and in Cynomolgus monkeys with a dose of 360 mg/kg/day (approximately equal to 1.8 times the highest recommended human dose in patients based on plasma AUC exposure), meropenem did not impair fertility. Also in the same studies meropenem was not teratogenic, but produced slight changes in fetal body weights at doses of 250 mg/kg/day and above.

Both meropenem and vaborbactam are primarily excreted in urine. However, in animal studies, systemic AUC exposures for vaborbactam and meropenem were not substantially altered when administered concomitantly, and neither agent as well as the hydrolyzed metabolite of meropenem was observed to accumulate with repeated dosing.

Reviewer Comment*: Pharmacology/Toxicology reviewer concluded that nonclinical pharmacokinetic and toxicity data for vaborbactam and meropenem do not indicate a potential for toxicity in the clinic above what is expected for treatment with meropenem alone.*

When vaborbactam was administered either as a single agent, or in combination with a carbapenem, no target organ toxicity was observed. Vaborbactam had no effect on male or female fertility or early embryonic development. Based on the short duration of clinical treatment, carcinogenicity studies were not conducted by the Applicant.

Photo toxicity studies were also not conducted by the Applicant since the molar extinction coefficient (MEC) of vaborbactam solutions did not exceed the threshold to trigger need for photo toxicity studies per ICH S10.

4.5. Clinical Pharmacology

The applicant has conducted six clinical studies that have included meropenem and/or vaborbactam that examined the PK properties of either or both compounds. A summary of those studies is displayed in Appendix-13.3.

4.5.1. Mechanism of Action

The meropenem component of meropenem-vaborbactam is a β-lactam antibacterial from carbapenem class. The bactericidal action of meropenem results from the inhibition of cell wall synthesis. Meropenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by gram negative and gram positive bacteria, with the exception of carbapenem hydrolyzing beta-lactamases. The vaborbactam component is a non-beta lactam, which is an inhibitor of Class A serine carbapenemases with a particular potent in vitro activity against *Klebsiella pneumoniae* carbapenemase, KPC. By inhibiting KPC and related beta-lactamases, vaborbactam protects meropenem from degradation by these enzymes.

4.5.2. Pharmacokinetics

The pharmacokinetics (Cmax and AUC) of meropenem and vaborbactam are linear across the dose range studied (1 g to 2 g for meropenem and 0.25 g to 2 g for vaborbactam) when administered as a single 3 hour intravenous infusion. There is no accumulation of meropenem or vaborbactam following multiple IV infusions administered every 8 hours for 7 days in subjects with normal renal function.

Absorption
Meropenem and vaborbactam are not expected to be absorbed systemically after oral administration.

Distribution
Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid (Merrem I.V. USPI). Vaborbactam is also widely distributed among tissues based on animal study. The highest mean drug-derived tissue concentration was found in the kidneys, prostate, urinary bladder, seminal vesicle and liver, and the lowest in the spinal cord and brain.
The plasma protein binding of meropenem and vaborbactam are approximately 2% and 33%, respectively.

Based upon the population PK analysis, the steady-state volume of distribution was similar for meropenem (20.2 L) and vaborbactam (18.6 L), indicating that both compounds distribute into a volume of distribution consistent with the extracellular fluid (ECF) compartment.

Meropenem is detectable at very low concentrations in animal breast milk (Merrem I.V. USPI). Meropenem-vaborbactam should not be used in breast-feeding women unless the potential benefit justifies the potential risk to breastfed children.

Metabolism and Elimination

Both meropenem and vaborbactam are primarily excreted via the kidneys as unchanged drug in the urine. Approximately 40% to 60% of a meropenem dose is excreted unchanged within 24 hours to 48 hours with a further 25% recovered as the microbiologically-inactive open lactam metabolite. Fecal elimination represents only approximately 2% of the dose. For vaborbactam, 75% to 95% of the dose is excreted unchanged in the urine over a 24-hour to 48-hour period.

A minor pathway of meropenem elimination is hydrolysis to an inactive open lactam metabolite via hydrolysis of the beta-lactam ring (meropenem open lactam), which accounts for approximately 28% of a meropenem dose. Vaborbactam is not metabolized.

In normal, healthy subjects, the terminal elimination half-life of meropenem and vaborbactam was approximately 1.0 h and 1.3 h, respectively. In subjects with renal impairment, the terminal elimination half-life for both meropenem and vaborbactam is prolonged, with the half-life for meropenem ranging from 1.4 hours in subjects with mild renal impairment to 5.7 hours in subjects with severe renal impairment and the half-life for vaborbactam ranging from 1.9 hours in subjects with mild renal impairment to 11.7 hours in subjects with severe renal impairment.

In a population PK analysis of plasma concentration data from subjects in the Phase 1 and Phase 3 trials, the post-hoc estimates of plasma clearance and elimination half-life were 10.5 L/h and 2.3 hours for meropenem, respectively, and 8.0 L/h and 2.2 hours for vaborbactam, respectively.

Drug-Drug Interactions

In a Phase 1 clinical trial (Study 501), concomitant administration of meropenem and vaborbactam did not affect the plasma or urine PK of either drug.

Neither meropenem nor vaborbactam are metabolized to a significant extent and thus, neither drug is expected to be involved in drug-drug interactions involving cytochrome P450 enzymes. Vaborbactam also has no meaningful activity as an inducer or an inhibitor of CYP450 enzymes, and no activity as an inhibitor or substrate of drug transporters.

Meropenem is a substrate for the organic anion transport (OAT) system, specifically OAT1 and

OAT3. Thus, probenecid competes with meropenem for active tubular secretion, resulting in increased plasma concentrations of meropenem [MERREM® I.V. USPI, 2016]. Co-administration of meropenem-vaborbactam with probenecid is not recommended.

Concomitant administration of meropenem and valproic acid has been associated with reductions in valproic acid concentrations with subsequent loss of seizure control. Thus, co-administration of meropenem-vaborbactam with valproic acid or divalproex sodium reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures. Supplemental anti-epileptic therapy should be administered when concomitant administration of valproic acid and meropenem-vaborbactam cannot be avoided.

4.5.3. Pharmacodynamics

The time that unbound plasma concentration of meropenem exceeds the meropenem-vaborbactam MIC against the infecting organism has been shown to correlate with efficacy in animal and in vitro models of infection. The ratio of the 24-hour unbound plasma vaborbactam AUC to meropenem-vaborbactam MIC is the index that predicts efficacy of vaborbactam in combination with meropenem in vivo and in vitro models of infection.

4.5.4. Population PK and PK-PD Analyses

A population PK model was developed using a dataset pooled from two Phase 1 studies (Study 501 and Study 504) and two Phase 3 studies (Study 505 and Study 506). The final analysis dataset included nearly 400 subjects and 4,000 plasma concentration-time observations for each compound. PK-PD analyses were conducted to examine the relationship between efficacy endpoints and meropenem and/or vaborbactam PK-PD indices using data from Phase 3 trials. These analyses demonstrated that 97% of patients with cUTI achieved the PK-PD target of free meropenem %T > MIC of 45% of the dosing interval, which has been associated with efficacy in nonclinical models of infection. Over 90% of patients with cUTI had free meropenem plasma concentrations that exceeded the MIC for 100% of the dosing interval.

PK-PD target attainment (PTA)

PK-PD target attainment analyses were conducted using Monte Carlo simulation, population PK models, and non-clinical PK-PD targets for efficacy for meropenem and vaborbactam, and in vitro surveillance data. The results demonstrated high probabilities of PK-PD target attainment at the upper margins of the MIC distributions for meropenem 2 g vaborbactam 2 g q8h and the equivalent dosing regimens adjusted for renal function. The probabilities of PK-PD target attainment based on a free meropenem percent of dosing interval that free plasma

concentrations exceed the indicated meropenem-vaborbactam MIC (%T>MIC) target of 45% were 94% or greater among simulated patients with cUTI or categorized by renal function group. These data provide support for a meropenem-vaborbactam PK-PD MIC breakpoint for susceptibility of 8 µg/mL (using fixed vaborbactam concentration of 8 µg/mL). At this breakpoint, 99.3% of Enterobacteriaceae, 99.5% of KPC-producing Enterobacteriaceae and 86.4% of *P. aeruginosa* isolates are inhibited.
Figure below presents FDA Clinical pharmacology reviewers' analysis.

Figure 1 PK/PD Target Attainment (PTA) at the Proposed 2g Meropenem – 2g Vaborbactam Dose Regimens

The Applicants' proposed susceptibility breakpoints for Enterobacteriaceae are supported by PTA analysis.

PK-PD Analysis for Efficacy

Patients with sufficient PK data from the ME populations from Study 505 and Study 506 were included in the Applicants' analysis for cUTI.
For patients with cUTIs, there were 175 patients within the ME population with sufficient PK data to enable post-hoc estimation of meropenem and vaborbactam PK parameters and exposures in the patients; of these, 154 patients had an Enterobacteriaceae as the baseline pathogen. Over 90% of patients with cUTI and among the subset of patients with Enterobacteriaceae achieved free-drug meropenem %T>MIC based on meropenem vaborbactam of 100%; 96.6 and 98.7% of patients with cUTI and the subset with Enterobacteriaceae respectively, achieved a non-clinical free-drug meropenem %T>MIC target

of 45%. The percentage of patients in these two populations that achieved successful responses for the efficacy endpoints assessed across study visits, including TOC, ranged from 93 to 100% for clinical response and 76.3 to 100% for microbiological response. Overall response at both EOIVT and TOC was 100 and 79% for patients with cUTI and the subset with Enterobacteriaceae, respectively. Thus, these analyses did not identify univariable PK-PD relationships for efficacy endpoints.
These analyses demonstrated that 97% of patients with cUTI achieved the plasma PK-PD target of free meropenem %T > MIC of 45% of the dosing interval, which has been associated with efficacy in nonclinical models of infection.

Reviewers' Comment: Analysis of probability of target attainment showed that 97% of patients with cUTI achieved the plasma PK-PD target of free meropenem %T > MIC of 45% of the dosing interval and the ratio of the 24h free vaborbactam AUC: MIC ratio was over 100-fold higher than nonclinical PK/PD targets. In addition, overall response at both EOIVT and TOC was 100% and 79% for patients with cUTI and the subset with Enterobacteriaceae, respectively. Due to the high target attainment rates to achieve PK/PD targets for both meropenem-vaborbactam along with high clinical and microbiological responses in these patients, high urinary drug concentrations in addition to the high systemic exposures, no univariate relationship between efficacy (clinical or microbiological response rates) and PK/PD targets could be identified.

4.5.5. Exposure-Safety Relationships

Exposure (AUC) to vaborbactam, meropenem and the metabolite of meropenem that were achieved in the toxicology studies of vaborbactam/meropenem at the highest dose levels tested, which are also the no-observed-adverse-effect-levels (NOAELs), are 2-7 fold the daily AUC achieved in humans when vaborbactam is administered in combination with meropenem at a combined dose of 2000 mg (2 g) for each entity and infused over a 3- hour period every 8 hours.
The safety margins calculated based on the human equivalent doses of vaborbactam and meropenem at the NOAEL doses in the 28-day toxicology studies, compared to the human dosing regimen of 2g every 8 hours, are shown in Table below.

Table 4 Vaborbactam and Meropenem Dose Margins for Humans Following Intravenous Administration of Meropenem 2g – Vaborbactam 2g Every 8 hours by 3 hour infusion based on Body Surface Area

Drug	Species	NOAEL (mg/kg/day)	NOAEL HED (mg/day)	Dose Margin 2 g q8h (6g/day)
Vaborbactam	Rat	1000	9677	1.6
	Dog	1000	33,333	5.6

Meropenem	Rat	500	4838	0.81
	Dog	500	16667	2.8
Source: Module 2.6.6. Toxicology Written Summary NOAEL HED = Study NOAEL X Human Weight (60kg) / Human to Animal Weight Factor (6.2 Rat; 1.8 Dog). NOAEL = No observed Adverse effect level; HED = human equivalent dose				

Exposure-Safety in Special Populations

Effect of Renal Insufficiency

Meropenem and vaborbactam are largely excreted as unchanged drug in urine. PK studies in uninfected subjects with varying degrees of renal impairment showed that the plasma clearance of meropenem and vaborbactam was reduced and was correlated with creatinine clearance (CrCl). As part of a population PK analysis of Phase 1 data (including subjects with renal impairment) and subjects enrolled in Phase 3 trials, a statistically significant relationship between plasma clearance of meropenem and vaborbactam and estimated glomerular filtration rate (eGFR) was developed. Based on these data, dosage regimens of meropenem-vaborbactam were developed for use in patients with varying degrees of renal impairment. In patients with end-stage renal disease (ESRD), hemodialysis removes both meropenem and vaborbactam.

Effect of Hepatic Impairment

Hepatic impairment has no effects on the PK of meropenem [MERREM® I.V. USPI, 2016]. Because vaborbactam is not appreciably metabolized, hepatic impairment is not expected to have an impact on the PK of vaborbactam. Therefore, the applicant has not studied vaborbactam in subjects with hepatic impairment.

Age, Weight, Gender, and Race

Population PK analysis (Studies 501, 504, 505, and 506) indicate that gender, age, body size, and race have no clinically relevant effect on the exposure of meropenem and vaborbactam. No dosage adjustment is warranted in these subpopulations.

4.6. Devices and Companion Diagnostic Issues

There is no companion diagnostic or device in this NDA.

4.7. Consumer Study Reviews

There have been no consumer safety reviews for meropenem-vaborbactam at the time this review was completed.

5 Sources of Clinical Data and Review Strategy

5.1. **Table of Clinical Studies**

The Applicant submitted five clinical studies in support of the NDA, including four Phase 1 studies (Study 501, Study 503, and Study 504 with meropenem-vaborbactam and Study 402 with vaborbactam only), a Phase 3 study in cUTI and pyelonephritis (Study 505), and a Phase 3 study in patients with CRE infections (Study 506). The latter study is ongoing and an interim data of 39 patients are submitted in the NDA.

The Phase 1 trials assessed the safety, tolerability, and PK of meropenem-vaborbactam. Study 504 examined whether or not a dose adjustment for meropenem-vaborbactam was required for subjects with renal impairment and Study 503 examined PK data in pulmonary epithelial lining fluid (ELF). The Study 505 was the single pivotal Phase 3 trial of meropenem 2 g-vaborbactam 2 g versus piperacillin/tazobactam for proposed indication in the treatment of cUTI, including pyelonephritis. Study 506 is an ongoing trial of meropenem-vaborbactam versus best available therapy (BAT) in the treatment of patients with severe gram-negative infections, suspected or known to be caused by KPC-producing CRE, including cUTI, cIAI, HABP, VABP, and bacteremia. The table below contains a summary of the trials in the Applicant's clinical safety database for meropenem-vaborbactam that were submitted with this NDA.

Table 5 Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route/Treatment Duration	Study Endpoints	F/U Visits	No. of Subjects	Study Population	No. of Sites /Countries
Controlled Studies to Support Efficacy and Safety							
Study 505	Phase 3, randomized, multicenter, double-blind, double dummy, parallel-group study of meropenem-vaborbactam versus piperacillin-tazobactam in the treatment of cUTI, including acute pyelonephritis (AP).	mer- 2 g Vab- 2 g IV q8h with each dose infused for 3 hours for up to 10 days Vs Pip- 4 g taz- 0.5 g IV infused in 100 mL normal saline over 30 min plus 250 mL normal saline IV infused over 3 hours q8h for up to 10 days After ≥15 IV doses, subjects could be switched to oral levofloxacin (500 mg q24h) to complete a total treatment course (IV plus oral) of 10 days. In case of levofloxacin resistance, T/S, cefdinir, and cefpodoxime could be used as step-down therapy. Treatment could go up to 14 days if clinically indicated in subjects with concurrent bacteremia.	The primary efficacy endpoints: The rates of overall success at the EOIVT in m-MITT population Secondary efficacy endpoint: -Overall success rate at both the EOIVT and TOC visits by infection type; - Cure rate at Day 3,EOIVT, EOT, TOC, and LFU by infection type; - Eradication rate at TOC	1. Day 3 of study Tx; 2. On last day of IV Tx [EOIVT], 3. On last day of total Tx [EOT]; 4. Test of Cure visit (EOT + 7 days); and 5. Late Follow-up visit (EOT +14 days).	550	Patients with cUTI, including AP	60 study sites in the following 17 countries: Brazil, Belarus, Bulgaria, Czech Republic, Greece, Hungary, Italy, Peru, Poland, Romania, Slovakia, Slovenia, South Korea, Spain, and Taiwan, Ukraine, United States.

Trial Identity	Trial Design	Regimen/ schedule/ route/Treatment Duration	Study Endpoints	F/U Visits	No. of Subjects	Study Population	No. of Sites /Countries
Other Studies to Support Safety							
Study 506	Phase 3, randomized, multicenter, open-label study of Mer-vab versus best available therapy (BAT) in the Tx of selected serious infections due to known or suspected CRE.	mer- 2 g vab- 2 g IV q8h, with each dose infused for 3 hours for 7 to 14 days Vs BAT with the following IV antibacterial drugs either in combination or alone for 7 to 14 days: carbapenem (meropenem, ertapenem, or imipenem),tigecycline, colistin, aminoglycosides (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam;	Efficacy endpoints for cUTI/AP: -Proportion of subjects with a clinical outcome of Cure at EOT and TOC; - Proportion of subjects with a microbiologic outcome of Eradication at EOT and TOC; -Proportion of subjects with overall success, a composite endpoint of clinical Cure and microbiologic Eradication, at EOT and TOC; -All-cause	Follow up for 28 days	41	Patients with cUTI or AP, cIAI, HABP, VABP, and bacteremia	

Trial Identity	Trial Design	Regimen/ schedule/ route/Treatment Duration	Study Endpoints	F/U Visits	No. of Subjects	Study Population	No. of Sites /Countries
			mortality rate at Day 28.				
Study 402	Phase 1, randomized, placebo-controlled, double-blind, SAD alone for first 6 cohorts, followed by MAD for remaining 4 cohorts	SAD Phase Placebo Vaborbactam 250 mg IV Vaborbactam 500 mg IV Vaborbactam 750 mg IV Vaborbactam 1 g IV Vaborbactam 1.25 g IV Vaborbactam 1.5 g IV MAD Phase Placebo Vaborbactam 250 IV q8h x 7 days Vaborbactam 1 g IV q8h x 7 days Vaborbactam 1.5 g IV q8h x 7 days Vaborbactam 2 g IV q8h x 7 days	Safety, tolerability, and PK of single and multiple IV doses of vaborbactam	7 days	80	Healthy adults	

Trial Identity	Trial Design	Regimen/ schedule/ route/Treatment Duration	Study Endpoints	F/U Visits	No. of Subjects	Study Population	No. of Sites /Countries
Study 501	Phase 1, randomized, placebo-controlled, double-blind, single- and multiple-ascending dose	mer-vab doses were 1 g-250 mg; 1 g/1 g; 1g-1.5 g; 1 g-2 g, and 2 g/2 g. SAD and MAD Phase (Q 8 h x 7 days)	Safety, tolerability, and PK of single and multiple IV doses of meropenem and vaborbactam	7 days	94 Placebo= (18) vab 250 mg = (8) vab 2g= (2) mer 1g= (16) mer2g= (5) mer 1g – vab 250 mg = (8) mer 1g vab 1g = (5) mer 1g vab 1.5g = (8) mer1g/vab 2g= (8) mer2g vab 2g (over 1-hr)= (8) mer2gvab 2g (over 3-hr)= (8)	Healthy adults	
Study 503	Phase 1, open-label epithelial lining fluid study	mer- 2 g vab- 2 g IV q8h × 3 doses	Safety and tolerability of 3 doses of mer-vab	Three doses	26	Healthy adults	

Trial Identity	Trial Design	Regimen/ schedule/ route/Treatment Duration	Study Endpoints	F/U Visits	No. of Subjects	Study Population	No. of Sites /Countries
Study 504	Phase 1, open-label, single-dose study of Mer-vab in subjects with varying degrees of renal impairment or insufficiency (RI)	M 1 g/V 1g IV, single dose	To evaluate safety and serum PK of a single dose of mer-vab in patients with RI and patients receiving HD as compared to normal HV	Single dose	41 HV =8 Mild RI =8 Moderate RI=8 Severe RI =8 ESRD =9	Healthy adults; Patients with renal insufficiency	
Abbreviations: mer: meropenem; vab: vaborbactam; Tx= treatment; T/S: Trimethoprim/sulfamethoxazole; *HV: Healthy Volunteers, SAD: Single ascending dose' MAD: multiple ascending doses; RI: Renal Insufficiency; ESRD: End Stage Renal Disease; HD: Hemodialysis; CRE=Carbapenem-resistant Enterobacteriaceae; cUTI=complicated urinary tract infection; d=days; h=hours; IV=intravenous; PK=pharmacokinetics;*							

5.2. **Review Strategy**

This application was submitted via the 505(b) (2) pathway, where the review of meropenem-vaborbactam relies upon the previous finding of safety and efficacy for meropenem, in addition to clinical, non-clinical, and animal models of infection data as a supportive evidence for the demonstration of the contribution of vaborbactam.

As stated in "combination rule" under section 21 CFR § 300.50, two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Special cases of this general rule are where a component is added:
– (i) to enhance the safety or effectiveness of the principal active component; and
– (ii) to minimize the potential for abuse of the principal active component.

For combination products, the evaluation of the contribution of individual components to the efficacy of the combination is required. When confirmatory clinical trials comparing the β-lactam alone to the combination product (β-lactamase inhibitor) are not feasible to evaluate the contribution of each component, supportive data from in vitro microbiology, PK/PD models, and animal studies can be used. Evidence from subgroups of patients with resistant pathogens can be described as well, when the BL-BLI combination is compared to the standard-of care.

Thus, the review will evaluate the efficacy and safety of meropenem-vaborbactam in the treatment of cUTI in all-comers, whereas the efficacy of the drug against CRE is supported by in vitro and animal data.

<u>General approach to this clinical reviewers' assessment of the evidence</u>

The reviewer will be presenting results of Applicant's analyses with clinical reviewers' commentary. The clinical reviewer collaborated with the statistician to confirm the results if there were discrepancies between Applicant and reviewers' assessment and went through numerous sensitivity analyses during the review process. Additional analyses by the clinical reviewer were conducted using inbuilt computer software such as JMP, JReview, and SAS etc. in order to more fully inform the reported results.

There were also significant interactions with the reviewers' from other disciplines including clinical pharmacology, pharmacology/toxicology, and chemistry manufacturing and controls reviewers during the review process. Reader is referred to the reviews from respective disciplines for discussion of *in vitro* microbiology results, animal data, Phase 1 trial, and pharmacokinetic/pharmacodynamic analyses, and product quality.

The review of clinical efficacy will primarily focus on the single pivotal Phase- 3 trial (Study -505) for c-UTI indication, and will be presented in section 6. The second Phase-3 trial (Study 506) was submitted by the Applicant as supportive evidence for cUTI indication. It was deemed inappropriate to pool the results of this trial to support efficacy in cUTI because this study differed from Study 505 with regard to study design and patient population. Study 506 is an open label trial in infections caused by CRE at various body sites and it is enrolling patients with significant comorbidities, more severe illness and higher mortality. Therefore, Study 506 will be reviewed briefly in section 6, and safety data from this study will be pooled for safety analysis and presented in section 8.

For the overall approach of safety review, individual clinical pharmacology studies from Phase-1 trials will not be reviewed in Section 6, because the study objectives of each study varied with regard to dose ranges, study design, and included vaborbactam, either alone or in combination with meropenem. The Phase 1 trials assessed the safety, tolerability, and PK of mer-vab and supported the use of meropenem 2 g-vaborbactam 2 g administered as a 3-hour IV infusion q8h in healthy volunteers. Discussion of results from these trials will focus on clinical safety analysis where appropriate and will be presented in section 8.

The majority of comparative safety data (i.e., adverse event rates) will be reviewed from Phase 3 trials (Phase-3 Pool) and pooled safety results from all Phase 1 and 3 trials (All Treated Pool). Overall safety review will be presented in section 8.

Section 7 of this document is not applicable to this application review, since, efficacy is mainly evaluated from the result of single adequate well controlled trial (Study 505) for the indication of cUTI which will be presented in section 6.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 505

6.1.1. Study Design

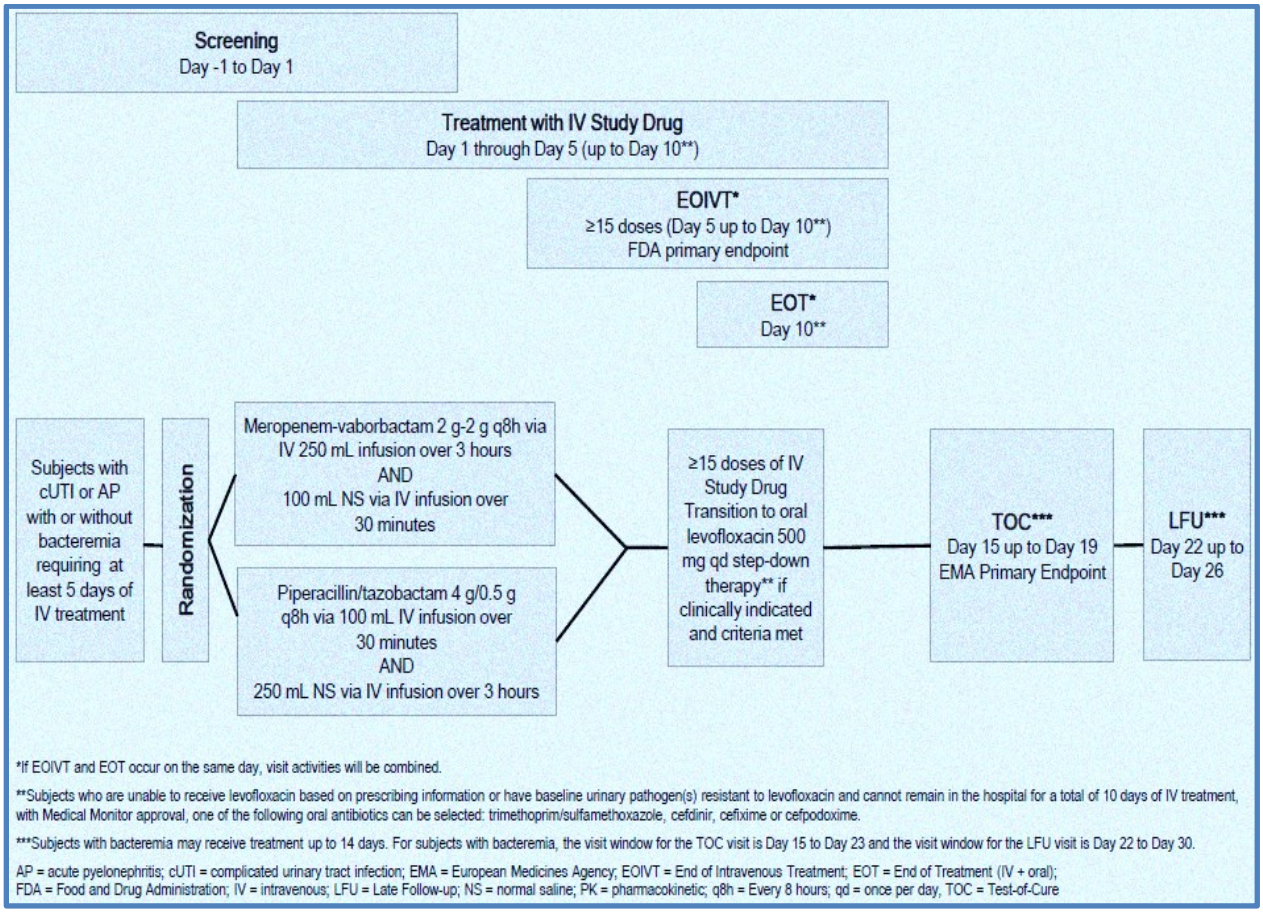
Overview and Objective

The objectives of this trial (Study 505) were to assess the efficacy and safety of meropenem-vaborbactam in subjects with cUTI or AP.

Trial Design

The Study 505 was a Phase 3, randomized, multi-center, double blind, double-dummy non-inferiority trial to evaluate the efficacy, safety, and tolerability of meropenem 2 g-vaborbactam 2 g (mer-vab) compared with piperacillin/tazobactam (pip-tazo) in the treatment of adults with cUTI or AP. The site pharmacist or designee was the only team member at the site level who was unblinded to treatment assignment to allow for preparation of study drug and this individual was not involved in any subject assessments. Figure 2 below displays the overview of schematic design of Study 505.

Figure 2 Overview of Study 505 Trial Design



Source: Clinical Study Report 505, Figure 1.

Patients were randomized in a 1:1 ratio to receive either mer-vab or pip-tazo. Patients in the mer-vab group received meropenem 2 g-vaborbactam 2 g diluted in normal saline to a volume of 250 mL and infused over 3 hours and to preserve the blind, 100 mL normal saline infused over 30 minutes q8h.
Patients in the pip-tazo group received piperacillin/tazobactam 4.5 g (piperacillin 4 g /tazobactam 0.5 g) diluted in normal saline to a volume of 100 mL and infused over 30 minutes

and to preserve the blind, 250 mL normal saline infused over 3 hours q8hr. Patients could switch to oral therapy after minimum of 15 doses of IV study drug if they met all step-down criteria for switching to oral therapy.

Levofloxacin 500 mg was administered orally q24h as a tablet(s). Patients who were either unable to receive levofloxacin based on prescribing information or who had baseline urinary pathogen(s) resistant to levofloxacin and could not remain in the hospital for a total of 10 days of IV treatment, other oral antibacterials e.g., trimethoprim-sulfamethoxazole, cefdinir, cefixime, or cefpodoxime were allowed to be used based on the urinary pathogen susceptibility. If the subject was bacteremic, they had to remain in the hospital for up to 14 days of IV treatment.

Reviewer Comment*: Piperacillin alone is approved for the treatment of urinary tract infections in US. Although piperacillin-tazobactam is approved for the treatment of cUTI in other parts of the world, it is not approved for this indication in US. However, it was allowed to be used as a comparator in this cUTI trial due to its antibacterial spectrum and PK properties. Other rationale to use piperacillin-tazobactam was that, it has bactericidal activity against primary pathogens that cause cUTI/AP, particularly Enterobacteriaceae, and exhibits time-dependent killing of bacteria, with three times per day dosing, and achievement of high urinary concentrations. The selected dose of piperacillin-tazobactam in this trial was 4.5 g q 8h whereas the usual daily dose of piperacillin-tazobactam in adults with a GFR of >40 mL/min is 3.375 q 6 h. This was discussed with the Division prior to initiation of this pivotal trial and based on FDA clinical pharmacology reviewers' analysis, it was deemed appropriate to be used at this dose in treatment of cUTI/AP for this trial.*

The dosage of mer-vab, pip-tazo, and oral levofloxacin used in this trial could be modified based on renal function, as shown in Figure 3 below. The dose modification for mer-vab in patients with renal impairment was based on the results of a separate renal impairment study (Study 504).

Figure 3: Dosage modification for renal impairment in Study 505

CrCl (mL/min)	Meropenem-Vaborbactam	Piperacillin/Tazobactam
≥50	2 g-2 g q8h	4.5 g q8h
≥30-49	1 g-1 g q8h	4.5 g q8h
CrCl (mL/min)	**Levofloxacin**	**Levofloxacin**
≥40	500 mg qd	500 mg qd
≥30-39	250 mg qd	250 mg qd

CrCl = creatinine clearance. Min = minutes. q8h = every 8 hours. Qd = once daily.

Source: Clinical Study Report 505, Table 2.

After at least 15 doses of intravenously therapy, patients could be switched to oral levofloxacin (500 mg q24h) based on investigator's judgement and signs and symptoms, provided that patients met following necessary criteria:

- Baseline organisms were sensitive to levofloxacin.
- Patient afebrile.
- Signs and symptoms of cUTI present at baseline were absent or had improved, with no new symptoms.
- Any leukocytosis present at baseline had improved or resolved.
- ≥1 urine culture negative for growth at 24 hours or exhibited growth with colony count $<10^4$ colony forming units (CFU)/mL.
- Subject was able to tolerate and absorb oral medications.
- Subject had no contraindications for levofloxacin in the investigator's opinion.
- Confirmed sterilization of the blood, if the subject had concurrent bacteremia.

The total duration of therapy (intravenous and oral) was scheduled for 10 days, excepting patients with concurrent bacteremia who could receive up to 14 days of total therapy.

Adjunctive non-study-specified antibiotic therapy administered with the intent of treatment of cUTI/AP, or other infection was not permitted under this protocol. However, patients in whom a resistant Gram-positive organism was suspected or identified could receive empiric coverage for gram-positive organisms, using an antibacterial drug with only gram-positive coverage (e.g., vancomycin, daptomycin, or linezolid).

Randomization was stratified based on *type of infection* (AP, cUTI with removable source of infection [e.g., Foley catheter], cUTI with non-removable source of infection [e.g., neurogenic bladder]) and *geographic region* (North America, Europe, Asia Pacific, Rest of the World). At least 30% of the study population was required to have diagnosis of AP. Enrollment of patients who had received a single dose of a short-acting oral or IV antibacterial agent for cUTI within 24 hours prior to randomization was limited to 25%.

Reviewers' Comment*: The study design was randomized, active controlled, double- blinded study, which is typical of the studies for the desired indication. The study design followed recommendations written in the Guidance for Industry on cUTI/AP.*

The duration of study participation for each subject was approximately 25 days, and consisted of:

a) Screening- 1 day

b) Study drug treatment while patients were on intravenous therapy, for up to 10 days (excepting subjects with concurrent bacteremia who could receive 14 days of total therapy).
c) An end of intravenous therapy (EOIV) visit between Day 5 and Day 10.
d) An end of therapy (EOT) visit on Day 10.
e) A test of cure (TOC) visit between Days 15-19.
f) A late follow-up (LFU) visit between Days 22-26.

An assessment of clinical outcome was performed on Day 3 of study treatment, on the last day of IV therapy (i.e., the End of IV Treatment [EOIVT]), on the last day of total therapy (i.e., End of Treatment [EOT]), at the Test of Cure (TOC) visit (EOT + 7 days), and at the Late Follow-Up (LFU) visit (EOT + 14 days). The visit activities at EOIVT and EOT were combined for patients who did not switch to oral therapy. If a subject withdrew from the study early, study assessments were performed at an early termination visit.

The protocol differentiated reasons for which study drug could be discontinued and reasons for which patients could be withdrawn from study assessments. Study drug administration could be discontinued at investigator discretion due to any medical condition or circumstance exposing the subject to potential risk or that did not allow adherence to protocol requirements, any adverse event (AE) or serious adverse event (SAE) that indicated study drug should be withdrawn, the subject's decision to withdraw, a requirement for prohibited concomitant medication, or lack of clinical improvement.

Any patients who prematurely discontinued study drug were asked to complete study assessments through the LFU visit, and EOT procedures were performed on the day of study drug discontinuation. Subjects could be withdrawn from study assessments due to loss to follow-up, the subject's decision to withdraw, withdrawal of consent for reasons other than adverse events, noncompliance or unwillingness to comply with protocol procedures, or termination of the study.

Following diagnostic criteria were required for enrollment of a patient in cUTI infection category:

Patient with signs / symptoms evidenced by at least TWO of the following:

i) Chills, rigors, or fever;
ii) Elevated white blood cell count(>10,000/µL) or left shift (>15% immature polymorphonuclear leukocytes);
iii) Nausea or vomiting;
iv) Dysuria, increased urinary frequency, or urgency;
v) Lower abdominal pain or pelvic pain;

AND

Pyuria as evidenced by ONE of the following:
i) Positive leukocyte esterase on urinalysis;
ii) White blood cell count >10 cells/µL in unspun urine;
iii) White blood cell count >10 cells/µL in urine sediment.

AND
Presence of at least one of the following associated risk factors:
i) Patients with an indwelling urinary catheter;
ii) Neurogenic bladder with presence or history of urine residual volume of >100 mL;
iii) Obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis) that is expected to be medically or surgically treated within 48 h post randomization;
iv) Azotemia due to intrinsic renal disease;
v) Urinary retention in men due to previously diagnosed benign prostatic hypertrophy.

Following diagnostic criteria were required for enrollment of a patient in AP infection category:
Patient with signs / symptoms evidenced by at least TWO of the following:
i) Chills, rigors, or fever;
ii) Elevated white blood cell count(>10,000/µL) or left shift (>15% immature polymorphonuclear leukocytes);
iii) Nausea or vomiting;
iv) Dysuria, increased urinary frequency, or urgency;
v) Flank pain;
vi) Costo-vertebral angle tenderness on physical examination;

AND
Pyuria as evidenced by ONE of the following features:
i) Positive leukocyte esterase on urinalysis;
ii) White blood cell count >10 cells/µL in unspun urine;
iii) White blood cell count >10 cells/µL in urine sediment.

The following <u>inclusion criteria</u> were required for enrollment:

1. A signed informed consent form.
2. Male or female age ≥18 years.
3. Body weight ≤185 kg.
4. Expectation, in the judgment of the investigator, that initial treatment with at least 5 days of intravenous antibiotics was warranted.
5. Documented or suspected cUTI (including AP) as defined above.
6. Expectation that any indwelling urinary catheter or instrumentation would be removed or replaced as soon as possible, and no longer than 12 hours after randomization.

7. Expectation that the subject would survive with effective antibiotic therapy and appropriate supportive care for the duration of the study.
8. Women of childbearing potential were required to have had a negative pregnancy test before randomization and be willing to use an effective method of contraception between randomization and 7 days after study participation.
9. Willingness to comply with all study procedures, whether in the hospital or after discharge, for the duration of the study.

Exclusion criteria selected for the protocol were as follows:

Exclusion criteria from the trial were stated as follows in the protocol:

1. Presence of any of the following conditions:
    a. Perinephric abscess
    b. Renal corticomedullary abscess
    c. Uncomplicated urinary tract infection
    d. Polycystic kidney disease
    e. Chronic vesicoureteral reflux
    f. Previous or planned renal transplantation
    g. Receiving hemodialysis
    h. Previous or planned cystectomy or ileal loop surgery
    i. Known candiduria
2. Presence of suspected or confirmed acute bacterial prostatitis, orchitis, epididymitis, or chronic bacterial prostatitis as determined by history and/or physical examination.
3. Gross hematuria requiring intervention other than administration of study drug.
4. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy).
5. Estimated creatinine clearance (CrCl) <30 mL/min using the Cockcroft-Gault formula.
6. Known nonretail source of infection such as endocarditis, osteomyelitis, abscess, meningitis, or pneumonia diagnosed within 7 days prior to randomization
7. Any of the following signs of severe sepsis:
    a. Shock or profound hypotension defined as systolic blood pressure <90 mmHg or a decrease of >40 mmHg from baseline (if known) that is not responsive to fluid challenge.
    b. Hypothermia (oral or tympanic temperature <35.6°C [<96.1°F] or rectal/core temperature <35.9°C [<96.6°F]).
    c. Disseminated intravascular coagulation as evidenced by prothrombin time or partial thromboplastin time >2X upper limit of normal (ULN) or platelets <50% of the lower limit of normal (LLN).
8. Pregnant or breastfeeding women.

9. History of epilepsy or known seizure disorder requiring current treatment with anti-seizure medication.
10. Treatment within 30 days prior to enrollment with valproic acid.
11. Treatment within 30 days prior to enrollment with probenecid.
12. Treatment within 30 days prior to enrollment with any cancer chemotherapy, immunosuppressive medications for transplantation, or medications for rejection of transplantation.
13. Evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis or hepatic encephalopathy.
14. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times upper limit of normal, or total bilirubin >1.5 times upper limit of normal.
15. Receipt of any investigational medication or investigational device during the last 30 days prior to randomization.
16. Prior exposure to vaborbactam alone or in combination with another product.
17. Receipt of any potentially therapeutic antibiotic agent within 48 hours before randomization, with the exception of the following:
    a. A single dose of a short-acting oral or intravenous antibiotic (an antibiotic that is typically dosed every 4 hours, every 6 hours, or q8h in a patient with normal renal function). The enrollment was restricted such that no more than 25% of subjects who met this criterion were to be enrolled.
    b. >48 hours of prior systemic antibiotic therapy for the current episode of cUTI, with unequivocal clinical evidence of treatment failure (i.e., worsening signs and symptoms).
    c. Developed signs and symptoms of cUTI or AP while on antibiotics for another indication.
18. Requirement at time of enrollment for additional systemic antibiotic therapy (other than study drug) or antifungal therapy for any reason. Topical antifungal or a single oral dose of any antifungal treatment for vaginal candidiasis was allowed.
19. Likely to require the use of an antibiotic for cUTI prophylaxis during the subject's participation in the study (from enrollment through the LFU visit).
20. Known history of human immunodeficiency virus infection with a CD4 count <200 cells/µL.
21. Presence of immunodeficiency or an immunocompromised condition, including hematologic malignancy, bone marrow transplant, or was receiving immunosuppressive therapy such as cancer chemotherapy, medications for the rejection of transplantation, and long-term use of systemic corticosteroids (equivalent to >20 mg a day of prednisone or systemic equivalent for ≥2 weeks).
22. Presence of neutropenia (<1,000 polymorphonuclear leukocytes/ µL).
23. Presence of thrombocytopenia (<60,000) platelets µL).
24. A corrected QT (QT_c) with Fridericia's formula (QT_cF) >480 milliseconds (msec).

25. History of significant hypersensitivity or allergic reaction to meropenem/vaborbactam, piperacillin/tazobactam, any of the excipients used in the respective formulations, or any beta-lactam antibiotics (e.g., cephalosporins, penicillins, carbapenems, or monobactams).
26. Known hypersensitivity or inability to tolerate all of the following: fluoroquinolones (including levofloxacin), trimethoprim/sulfamethoxazole, cefdinir, cefixime, or cefpodoxime based on prescribing information.
27. Unable or unwilling, in the judgment of the investigator, to comply with the protocol.
28. An employee of the investigator or study center with direct involvement in the proposed study or other studies under the direction of that investigator or study center, or a family member of the employee or the investigator.
29. Acute Physiology and Chronic Health Evaluation (APACHE) II score >30. An APACHE II score was only required if calculated.
30. Inability to tolerate IV fluids of 1050 mL per day required for study drug administration because of medical reasons.
31. Any recent history of trauma to the pelvis or urinary tract.

Reviewer Comment*: The inclusion and exclusion criteria were appropriate. Patients with diagnosis of seizures or on seizure medication were required to be excluded since there is an increased risk of seizures associated with a carbapenem class of antibacterial drugs. Warnings on the risk of seizures associated with meropenem-vaborbactam are expected to be included in the product label, similar to the other carbapenems.*

Patients with renal impairment were initially excluded from the study. The protocol was amended later based on the results of the renal impairment study (Study 504), and the eligibility criteria were modified to allow patients to be included in the study with estimated creatinine clearance > 30 mL/min. However, patients with creatinine clearance < 30 ml/min were excluded. The label of the meropenem-vaborbactam may need to include information on insufficient efficacy and safety data for the product in patients with severe renal impairment.

Dosage Regimen Selection

The dosing regimen of meropenem 2 g and vaborbactam 2 g was chosen based on PK/PD targets. Meropenem was found to attain the target PK-PD exposures in 100% of simulated patients with MICs above the current nonsusceptible MICs of ≥4 µg/mL. Additionally, *in vitro* PD and resistance development studies using a hollow fiber model simulating a regimen of meropenem 2 g-vaborbactam 2 g administered q8h by 3-hour infusion were able to treat organisms with MIC of 8 µg/mL and prevent development of resistant subpopulations in carbapenem-resistant *Klebsiella pneumoniae* (*K. pneumoniae*) and *P. aeruginosa.* When exposures corresponding to 1 g meropenem-1g vaborbactam administered q8h by 3-hour

infusion against the same strains were tested, suboptimal killing and emergence of resistance was noted. Therefore for this study a dose of meropenem 2 g-vaborbactam 2 g given as a 3-hour infusion q8h was chosen to demonstrate safety and efficacy of the combination. The dose modification for meropenem-vaborbactam in patients with renal impairment was based on the results of a Phase 1 renal impairment trial, Study 504. A dose modification was required for meropenem-vaborbactam in patients with an estimated CrCl < 50 mL/min.
No dose adjustment was required for piperacillin/tazobactam for these subjects. A reduced dose of oral levofloxacin was required for subjects with an estimated CrCl less than 40 mL/min.

The table below summarizes the schedule of assessments and procedures for study 505.

Table 6 Schedule of Assessments and Procedures- Study 505

	Screening	Treatment							Follow-Up		
Day Assessment/Procedure	-1 or 1[a]	1[a] pre-dose	1[a] post-dose	2	3	4-10[b]	EOIVT (+1 day) Day 5-10[b]	EOT Day 10 (+1 day)[b]	TOC EOT + 7 days (±2 days)[c]	LFU EOT + 14 days (±2 days)[d]	Early Termination[e]
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Medical/surgical history and non-pharmacologic procedures	X										
Prior/concomitant medications	X	X		X	X	X	X	X	X	X	X
Demographics[f]	X										
Height and weight	X										
Complete physical examination	X								X		X
Limited physical examination[g]					X		X	X		X	
Vital signs[h]	X	X			X		X	X	X	X	X
Assess signs/symptoms[i]	X	X		X	X	X	X	X	X	X	X
Assessment of clinical outcome					X		X	X	X	X	X
Randomization to treatment arm		X									
Pregnancy test[j]	X	X						X[j]			X[j]
Screening labs[k] (Local labs)	X										
Hematology[l] (Central labs)		X			X		X	X	X	X	X
Serum chemistry[m] (Central labs)		X			X		X	X	X	X	X
Urinalysis[n] (Central labs)		X			X		X	X	X	X	X
Pharmacokinetic sampling[o]			X		X		X				
12-lead ECG[p]	X	X	X		X		X				X
Blood cultures[q]	X										
Urine cultures[r]	X				X		X	X	X	X[r]	X
Other cultures[s]	X										
Study drug administration[t]			X	X	X	X	X	X			
Assessment of adverse events	X	X	X	X	X	X	X	X	X	X	X

a. Screening procedures may be performed up to 24 hours prior to the first dose of study drug. All screening procedures must be completed prior to randomization and the first dose of study drug.
b. If EOT and EOIVT occur on Day 10, visit activities will be combined. Subjects with concurrent bacteremia may receive up to 14 days of treatment.
c. The TOC visit will occur between Day 15 and Day 19. For subjects with bacteremia, the TOC visit window is Day 15 to Day 23.
d. The LFU visit will occur between Day 22 and Day 26. For subjects with bacteremia, the LFU visit window is Day 22 to Day 30.
e. Subjects are expected to complete all study visits. In circumstances where a subject discontinues the study early, an early termination visit will be performed.
f. Demographic data will be collected, including name, sex, age, race, ethnicity, BMI, alcohol use, and nicotine use.
g. A limited, symptom-based, physical examination will be performed at indicated visits. If a subject does not display symptoms, no limited physical examination needs to be performed.
h. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
i. Assessment of signs and symptoms will include assessments to classify the following as new onset, continuing (increased, decreased, no change), or resolved (returned to pre-infection baseline or pre-infection condition): fever (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]), urinary frequency, urinary urgency, dysuria, nausea, vomiting, abdominal pain, supra-pubic pain or discomfort, flank pain, and costo-vertebral angle tenderness on examination
j. At Screening, a urine pregnancy test will be performed locally and on Day 1 (Pre-dose) a serum pregnancy test will be performed at the central lab on women of childbearing potential only. A urine and serum pregnancy test will be performed at EOT for women of childbearing potential. If a subject discontinues the study early, a urine and serum pregnancy test will be performed if the woman is of childbearing potential.
k. Screening laboratory tests will include AST, ALT, creatinine, WBC count with differentials, platelet count, and LCE in urine. All screening laboratories will be performed at the local laboratory.
l. Hematology parameters include complete blood count (red blood cell count, WBC count with manual differentials, platelet count, hemoglobin, and hematocrit).
m. Serum chemistry parameters include at a minimum: creatinine, creatinine clearance, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, uric acid, lipase, creatine kinase, amylase, albumin, lactate dehydrogenase, total protein, carbon dioxide, glucose, sodium, potassium, chloride, calcium, and phosphorus.
n. Urinalysis includes dipstick analysis of protein, glucose, ketones, bilirubin, blood, nitrites, and urobilinogen; microscopic evaluation for red blood cells, WBCs, bacteria, and casts; specific gravity; leukocyte esterase and pH.
o. Pharmacokinetic blood samples on Day 1 will be taken 3 to 3.5 hours and 5 to 6 hours after the START of the first 3-hour IV study drug infusion. Pharmacokinetic blood samples on Day 3 and EOIVT will be taken 3 to 3.5 hours after the START of one of that day's 3-hour IV study drug infusions. Samples will not be collected around the 30-minute infusions. Pharmacokinetic sampling and triplicate 12-lead ECGs should be performed around the same 3-hour infusion.
p. All subjects will have triplicate 12-lead ECGs performed at screening and on Day 1, Day 3, and EOIVT at pre-dose and 15 minutes (±15 minutes) after the completion of one of that day's 3-hour infusions. Pharmacokinetic sampling and triplicate 12-lead ECGs should be performed around the same 3-hour infusion. If the early termination visit occurs prior to EOIVT, triplicate ECGs should be performed.
q. Two sets of samples from 2 separate venipuncture sites will be obtained prior to randomization for baseline blood cultures. For those where a pathogen is identified, susceptibility testing will be performed. If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, subsequent, daily blood cultures will be collected until the first negative blood culture (culture reading at 24 hours or more). Additional blood cultures will be collected at the Investigator's discretion. For subjects with fever spikes (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature ≥38.3°C [≥100.9°F]), additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and susceptibility testing, and any isolates will be frozen and sent to the central laboratory (b) (4) for confirmation.
r. Urine samples should be collected by clean-catch midstream, from a newly-inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, or ureter aspiration at the specified time points. An additional urine culture should be obtained at the LFU visit, if clinically indicated. The baseline urine sample submitted for culture must have a microscopic evaluation (e.g., Gram stain) and a dipstick analysis performed by the local laboratory. Specimens will be sent to the local laboratory for culture and susceptibility testing and any pathogens will be frozen and sent to the central laboratory (b) (4) for confirmation. A repeat urine sample for culture must be obtained before the start of study drug therapy for subjects enrolled after receiving a single dose of a short-acting antibiotic or for subjects who failed preceding antimicrobial therapy.
s. If clinically indicated, a tissue sample (i.e., kidney biopsy) will be collected prior to randomization. In the event that pre-randomization urine and blood cultures are negative and the subject has a positive tissue culture, the isolated pathogen may qualify as a defined baseline pathogen. The isolated pathogen should be shipped to the central laboratory (b) (4) for confirmation and susceptibility testing.

Source: Module 5.3.5.1, 505- Study Protocol

6.1.1.1. 6.1.1.1 Study Endpoints

The primary endpoint for this study was the proportion of patients in the microbiological modified intent-to-treat (m-MITT) population, who achieve Overall Success at the EOIVT visit.

The m-MITT population was defined as all randomized subjects who received any dose of study drug and had a baseline bacterial pathogen of $\geq 10^5$ CFU/mL on urine culture, or the same bacterial pathogen was present in concurrent blood and urine cultures.

The Overall Response was a composite endpoint requiring clinical cure or improvement, and microbiological eradication (or in some cases presumed eradication) as specified in the table below.

Based on the following signs and symptoms of cUTI or AP at the pre specified time points (see schedule of assessments and procedures, Table 6) and categorizing each of the following signs and symptoms as either new onset, continuing (increased, decreased, no change), or resolved (returned to a pre-infection baseline or pre-infection condition), Clinical Outcome endpoints were determined. It also involved overall investigator judgment whether continued antibacterial therapy was warranted.

- Fever (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal/core temperature
- ≥38.3°C [≥100.9°F])
- Urinary frequency
- Urinary urgency
- Dysuria
- Nausea
- Vomiting
- Abdominal pain
- Supra-pubic pain or discomfort
- Flank pain
- Costo-vertebral angle tenderness
-

Table 7 Criteria for Clinical Outcome

Cure	At EOIVT, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP. At EOT, TOC, and LFU, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP such that no further antimicrobial therapy was warranted. Symptom resolution did not necessarily include baseline symptoms associated with anatomic abnormalities that predisposed to cUTI such as symptoms associated with the presence of an indwelling urinary catheter. This outcome category was used only at the EOIVT, EOT, TOC, and LFU visits.

Improvement	Lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms of cUTI or AP, but continued IV therapy was warranted. This outcome category was used only at Day 3 and the EOIVT visits.
Failure	Subjects who experienced any **one** of the following: ➢ At any study visit, worsening of baseline clinical signs and symptoms of cUTI or AP or the development of new clinical signs and symptoms of infection, sufficient to stop study drug and initiate a non-study antimicrobial; ➢ At EOT, TOC, and LFU visits, persistence, incomplete resolution of baseline clinical signs and symptoms of infection; ➢ Withdrawal from the study due to an AE or due to lack of clinical improvement; ➢ Death of the subject during the study
Indeterminate	Clinical outcome cannot be determined.
AE = adverse event; AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOIVT = End of Intravenous Treatment; EOT = End of Treatment; IV = intravenous; LFU = Late Follow-Up; TOC = Test of Cure.	

The protocol defined Microbiology Outcome as specified in the table below. Of note, different microbiological criteria were used by the Applicant for the Food and Drug Administration (FDA) and European Medicines Agency (EMA), however, this review focuses only on the FDA definitions. The urine and blood cultures were to be taken at baseline, but treatment was initiated before microbiological identification of the causative pathogen. Each baseline organism was classified by the Applicant as either a pathogen (i.e., causative pathogen for cUTI) or a non-pathogen. The Microbiological Outcome could not be properly defined for subjects who did not have a baseline pathogen. Table 8 and Table 9 define the Criteria for Microbiological Outcome and Overall Response at EOIVT visits.

Table 8 Criteria for Microbiological Outcome

Eradication	Baseline bacterial pathogen(s) was reduced to $<10^4$ CFU/mL on urine culture ; AND A negative blood culture for an organism that was identified as a uropathogen (if repeated after positive at BL blood culture)
Persistence	One or more of the baseline bacterial pathogen(s) was continuously present at $>=10^4$ CFU/mL on urine culture ; OR A continuously positive blood culture with an organism that was identified as a uropathogen
Recurrence	Isolation of the same baseline bacterial pathogen(s) from culture after a response of eradication OR A positive blood culture with the same BL organism that was identified as a uropathogen after a response of eradication
Indeterminate	No urine culture or the urine culture could not be interpreted for any reason
BL: Baseline, CFU = colony forming units, FDA = Food and Drug Administration.	

Table 9 Overall Response at EOIVT Visit

Clinical Outcome	Microbiologic Outcome			
	Eradication	**Persistence**	**Recurrence***	**Indeterminate**
Cured	Success	Failure	Failure	Success based on presumed eradication
Improvement	Success	Failure	Failure	Success based on presumed eradication
Failure	Failure	Failure	Failure	Failure based on presumed eradication
Indeterminate	Failed if clinical outcome at Day 3 =failed; otherwise = Indeterminate	Failure	Failure	Failed if clinical outcome at Day 3 =failed; otherwise = Indeterminate
*For an outcome of recurrence, patients must have had documented prior eradication (i.e., Day 3) based on FDA's CFU/mL criterion of $<10^4$ CFU/mL of urine.				

***Reviewers' Comment**: This primary endpoint of Overall Response is in accordance with the recommendations made in the Guidance for Industry on Complicated Urinary Tract Infections: Developing Drugs for Treatment, February 2015. The guidance states that "Microbiological success is an important component of the responder endpoint because the ascending route of infection is the most common pathophysiological mechanism for cUTI. Continued bacteriuria at greater than 10^4 CFU/mL in patients recently completing treatment for cUTI represents a known risk for enhanced rate of relapse of cUTIs. Hence, microbiological success, along with resolution of symptoms, is the evidence chosen to support a conclusion of treatment benefit."*

The selection of EOIVT visit for primary endpoint was based on the thinking that noninferiority assessments of meropenem-vaborbactam at later study visits could be complicated or confounded by the use of oral therapy. However, there were few drawbacks with selection of this endpoint as the single primary endpoint which will be discussed later in results section. The FDA guidance document on developing antibacterial drugs for complicated urinary tract infections released in 2015, recommends that when a drug only has an intravenous formulation, the trial should use co-primary endpoints at time points defined at a fixed time point after completion of the total duration of antibacterial therapy (both intravenous and oral therapy) plus a period of 5-7 days observation after completion of antibacterial drug therapy (which is usually called Test of Cure visit). The reason to make both assessments is that the results at the EOIV visit are not affected by oral therapy, while sustained response after a period of observation after completion of treatment is considered more clinically meaningful. Study 505 only defined a single primary endpoint at the EOIV visit because the trial began before the FDA guidance was finalized.

The secondary endpoints for this study are listed below:

- Proportion of subjects in the m-MITT Population with overall success at both the EOIVT and TOC visits;
- Proportion of subjects in the m-MITT and ME Populations with a microbiologic outcome of Eradication to $<10^4$ CFU/mL of urine for FDA at Day 3, EOIVT, EOT, TOC, and LFU;
- Proportion of subjects with a clinical outcome of Cure in the m-MITT, Clinical Evaluable (CE), and ME Populations at Day 3, EOIVT, EOT, TOC, and LFU;

The Safety endpoints included adverse events (AEs), AEs of special interest based on AEs noted in the warnings and precautions for meropenem (hypersensitivity, *Clostridium difficile*-associated diarrhea, and seizure), deaths, serious adverse events (SAEs), discontinuation of study drug or the study due to an AE, clinical laboratory evaluations tests (hematology, serum chemistry, and urinalysis), vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), and electrocardiograms.
An independent Data Safety Monitoring Board (DSMB) was to review serious adverse events on an ongoing basis, and review accumulated safety data for this study and Rempex-506 when the study enrollment reaches approximately 40% and 75%.

]

6.1.1.2. 6.1.1.2 Statistical Analysis Plan

Efficacy Analysis

Analyses of efficacy variables were performed separately for the MITT, m-MITT, CE, and ME Populations. The primary statistical objective of this trial was to determine whether mer-vab is non-inferior to pip-tazo in adult subjects with cUTI or AP. The primary endpoint was proportion of subjects in the m-MITT Population with overall success at the EOIVT visit (Cure or Improvement + Eradication at EOIVT). The non-inferiority margin was a difference of 15 percentage points. The non-inferiority assessment was based on the two-sided 95% CI for the difference in the proportions of subjects, based on the endpoints, calculated as the rate in the meropenem-vaborbactam group minus that of the piperacillin-tazobactam group. Non-inferiority was to be concluded if the lower limit of the two-sided 95% CI is > - 15%. If non-inferiority was demonstrated, an assessment for superiority was to be performed.

Reviewers' Comment*: The NI margin chosen was wider than the 10% margin recommended in the current Guidance for Industry on cUTI, February 2015. This trial was designed with a non-inferiority margin of 15%, with the FDA advice that this margin may only support an approval with "limited use" language on labeling.*

Safety Analysis

Safety was evaluated by presenting summaries of treatment-emergent adverse events, routine clinical laboratory evaluations, ECGs, vital signs, and physical examination findings for each treatment group. All safety analyses were performed using the Safety Population.

Analysis Populations

The Intent-to-Treat (ITT) Population included all patients screened and randomized to study drug (meropenem-vaborbactam or piperacillin/tazobactam).

The Modified Intent-to-Treat (MITT) Population included patients who meet the ITT criteria and receive at least one dose of study drug. Analyses for the MITT were performed according to randomized treatment.

The Safety Population included patients who met the ITT criteria and received at least one dose of study drug, based on actual treatment received.

The Microbiological Modified Intent-to-Treat (m-MITT) Population included patients who met the MITT criteria and had a baseline bacterial pathogen(s) of $\geq 10^5$ CFU/mL of urine in baseline urine culture or the same bacterial pathogen present in concurrent blood and urine cultures. Patients who only have an identified Gram-positive pathogen in the urine and have received > 48 hours of an antibiotic with only Gram-positive coverage were not supposed to be included in the m-MITT population.

The Clinical Evaluable (CE) Population included patients who met the MITT criteria and had no key inclusion or exclusion violations; obtained a clinical outcome (Cure, Improvement, or Failure) at EOIVT, unless criteria for Failure were met at an earlier time point; received ≥80% of expected IV doses for the completed treatment duration, missed no more than 1 IV dose in the first 48 hours of treatment, and missed no more than 2 consecutive IV doses overall, and received ≥6 doses of study drug if classified as a Failure on clinical outcome, or received ≥9 doses of study drug if classified as a Cure on clinical outcome.

The Microbiologic Evaluable (ME) Population included patients who met the MITT criteria and had a bacterial pathogen(s) of $\geq 10^5$ CFU/mL of urine at baseline urine culture for evaluation or had same bacterial pathogen present in concurrent blood and urine cultures, have no key inclusion or exclusion violations; obtain a clinical outcome (Cure, Improvement, or Failure) and microbiologic outcome (Eradication or Persistence) at EOIVT, unless criteria for Failure were met at an earlier time point; received ≥ 80% of expected IV doses for the completed treatment duration, missed no more than 1 IV dose in the first 48 hours of treatment, and missed no more than 2 consecutive IV doses overall; and received ≥6 doses of study drug if classified as a Failure on overall outcome, or received ≥9 doses of study drug if classified as a Cure on overall outcome.

Reviewers' Comment: *The analysis population used for the primary efficacy analysis was the microbiological modified intent-to-treat (m-MITT) population of patients with a microbiologically confirmed baseline pathogen who received at least a single dose of study drug.*

Protocol Amendments

There were three amendments to the study 505 protocol, which are outlined below.

Protocol Amendment #1: The first protocol amendment added dose adjustments for renally insufficient subjects. It included the use of trimethoprim/sulfamethoxazole, cefdinir, and cefpodoxime as step-down therapy for levofloxacin resistant subjects. It required an APACHE II score <30 in subjects who have a calculated APACHE II score. It included a Data Safety Monitoring Board and it removed urinary incontinence, pyuria, and lower back pain from the list of signs and symptoms.

Reviewers' Comment*: This amendment was made based on FDA recommendations to enroll patients with renal impairment, particularly due to the fact that more severe infections and infections caused by resistant microorganisms are more likely to occur in patients with co-morbidities. Based on the results of the renal impairment study, sponsor has modified the eligibility criteria to allow patients to be included in the study with renal function at screening as estimated by creatinine clearance of up to > 30 mL/min using the Cockcroft-Gault formula. FDA also recommended that oral switch in patients with bacteremia may not be appropriate, therefore, these patients should complete 10-14 days of IV therapy without switching to an oral drug.*

Protocol Amendment #2: The second amendment modified the percentage of patients with acute pyelonephritis to at least 30%, and modified weight criteria up to 185 kg. It allowed the use of one dose of a short-acting antibacterial drug within 24 hours of randomization in up to 25% of subjects and allowed for antibacterial coverage of any gram-positive organisms. It excluded subjects with recent history of trauma to the pelvis or urinary tract. It added collection of presence or history of Charlson Comorbidity Components to the subject's medical history.

Reviewers' Comment*: Key changes in this amendment were made based on the Guidance for Industry (Complicated Urinary Tract Infections and Pyelonephritis - Developing Drugs for Treatment. February 2015), including addition of criteria for enrollment of at least 30 percent of the patient population with diagnosis of acute pyelonephritis, and exclusion of patients who had a recent history of trauma to the pelvis or urinary tract.*

Protocol Amendment #3: The third amendment included change in sample size from 850 patients to 500 patients, with corresponding changes to the inferiority margin of 10% to 15%. The stipulation of "gram negative" from the analysis populations section was removed in this amendment.

Reviewers' Comment*: Based on discussions with the FDA, at the September 30, 2015 meeting, the sample size was changed from approximately 850 patients to approximately 500 patients, with corresponding changes to the inferiority margin of 10% to 15%. Another change based on agreement was removal of the stipulation of "gram negative" from the analysis populations as meropenem and piperacillin/tazobactam both have activity against gram positive bacteria, it was granted that patients with gram negative and/or gram positive organisms will be included in the m-MITT and ME populations as long as patients did not receive a gram positive antibacterial drug for additional coverage.*

Data Quality and Integrity: Sponsor's Assurance

The investigator was required to maintain accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The investigational sites were visited by the study monitor on an average of every 6 to 8 weeks. During their visits, the monitors inspected the electronic Case Report Form (eCRF) to ensure adherence to the protocol and verify the data by comparison with source documents. All the data were recorded on the eCRF and were verified by a series of computerized edit checks. The data were also remotely reviewed by the Applicant's data managers. The Applicant attests that all discrepancies were reviewed and any resulting queries were resolved with the investigator and amended on the clinical database and were documented in an audit trail.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP). Overall, 60 study sites in the 17 countries received IRB/IEC approval to conduct the study randomizing at least 1 subject: Brazil, Belarus, Bulgaria, Czech Republic, Greece, Hungary, Italy, Peru, Poland, Romania, Slovakia, Slovenia, South Korea,

Spain, and Taiwan, Ukraine, United States.

Financial Disclosure

Please see the financial disclosure review form in Appendix 13.2.

Reviewers' Comment*: Applicant has adequately disclosed financial interests/ arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. Financial disclosure of all "covered clinical studies," as defined in 21 CFR Part 54 was reviewed by this reviewer. There was no conflict of financial interest noted for any of the study investigators.*

6.1.3. Patient Disposition

Study 505 was planned to enroll approximately 500 patients; however, the final sample size was 550 randomized patients. Of those 550 patients, 274 were randomized to mer-vab and 276 to pip-tazo. Of 274 patients in the mer-vab group, 272 received at least one dose of study drug (MITT Population), whereas 273 patients received at least one dose of study drug in the pip-tazo group (MITT population). Overall, a similar percentage of subjects with AP (59.2% and 59.0%) and cUTI (40.8% and 41.0%) were enrolled in each group.

Reviewers' Comment*: The agreed upon planned enrollment for the protocol was approximately 500 patients in the ITT population. An information request was sent to the sponsor to justify the change in the sample size. Sponsor clarified that "they over enrolled subjects by 10% to be on conservative side to ensure that the required minimum safety database of at least 300 patients exposed to meropenem-vaborbactam at the intended dose is achieved". This was acceptable to the Division since this was done while sponsor was still blinded to the study results.*

This reviewer explored the reason for 5 patients (2 in mer-vab and 3 in pip-tazo group), not to receive any dose of study drug. Patient # 112-007-505 and # 804-008-503 refused to remain in the study after enrollment; patient # 300-001-502 withdrew consent within 5 minutes of enrollment; patient # 616-004-501 was randomized by mistake, since it was discovered later (prior to receiving study drug) that he did not meet inclusion criteria; patient # 804-001-529 refused to receive study treatment after enrollment.

Most patients in the MITT (safety) population completed study treatment (91.5% in the mer-vab and 86% in pip-tazo group). The completion of study treatment included both IV and oral step-down therapy. Similarly, among the m-MITT (efficacy) population, 95%, and 88%, respectively in the mer-vab and pip-tazo group completed study treatment. Of the patients who did not complete study treatment, most were premature discontinuation of IV therapy in both

groups (8.1% and 12.8% in the mer-vab and pip-tazo group, respectively). Most common reasons for discontinuation of treatment were physician decision (8 [3%] in the mer-vab and 13 [5%] in pip-tazo group), followed by adverse events (4[2%] in mer-vab and 7[5%]) pip-tazo group, respectively).

The majority of patients completed the study irrespective of treatment duration in both treatment groups (about 95% and 92% in the mer-vab and pip-tazo group, in the MITT population and 95% and 93% respectively in the m-MITT population). The primary reasons for not completing the study in the mer-vab and pip-tazo group were lost to follow-up (5 [2%] and 10 [4%], respectively), and subject withdrawal (5 [2%] and 7[3%], respectively), followed by an AE (3[1%] each group).

Table below displays the disposition of patients in the safety (MITT) and efficacy (mMITT) population.

Table 10 Disposition of patients (m-MITT Population)

	m-MITT	
	mer-vab (n=192) n (%)	**pip-tazo (n=182) n (%)**
Patients who completed study treatment	182 (94.8)	161 (88.5)
Patients who did not complete study drug treatment	10 (5.2)	21 (11.5)
Reasons for Not completing Study Treatment		
Physician decision	4 (2)	9 (5)
Withdrawal by subject	3 (2)	2 (1)
Adverse event	3 (2)	8 (4)
Lack of Efficacy	0 (0)	1 (0.5)*
Other	0 (0)	0 (0)
Lost to follow-up	0 (0)	1 (0.5)
Subjects who did not complete IV study treatment	10 (5)	19 (10)
Subjects who started oral step-down study treatment	117 (61)	94 (52)
Subjects who were started on oral step-down but did not complete the oral treatment	0 (0)	2 (2)
Subjects who completed the study	183 (95)	169 (93)
Subjects who did not complete the study	9 (5)	13 (7)
Reasons for not completing the Study		
Lost to follow-up	5 (3)	6 (3)
Withdrawal by subject	2 (1)	3 (2)

Adverse event	2 (1)	3 (2)
Physician decision	0 (0)	0 (0)
Other	0 (0)	1 (0.5)
Source: Clinical Reviewers' Analysis, , eCRF **Subject ID: 300-001-518: This patient is classified by the Applicant as 'lack of efficacy', however, CRF review suggests that the patient withdrew from the study since the patient did not want to undergo study procedures as required in the protocol.*		

Reviewers' Comment*: This reviewer investigated the details of all patients who discontinued the study treatment for any reason(s). There were almost twice the numbers of treatment discontinuation due to physician's decision in the pip-tazo group as compared to mer-vab group. The term "Physician discontinuation" could be misleading, as it could mean intolerance to the study drug or other reasons that led the investigator to think that the patient is not suitable for continuing therapy. This term does not clarify why the study drug was discontinued by the physician. On further exploration of CRFs, this reviewer found that in both mer-vab and pip-tazo group, the most common explanations for physicians to discontinue the study treatment prematurely was either "patient returned to good clinical status" early and the investigator felt that further treatment was not indicated or patients returned to good clinical status, however, patients were found to have pathogens resistant to levofloxacin. One study site (300-001) was noted to have discontinuations by physician due to the fact that patients returned to good clinical status at an earlier time point and investigators were not clear about oral options other than levofloxacin for patients who were allergic to this drug. Some sites were not clear about the requirement of the protocol to complete 10 days of total treatment; therefore, patients were discontinued from IV therapy and were discharged early as soon as they were clinically improved or cured.*

Physician discontinuations has also impacted IV treatment completion and switch to oral therapy. This has led to higher number of patients in the pip-tazo group not completing IV study treatment and subsequently not switching to oral therapy as compared to the mer-vab group.

Disposition for patients in the MITT population is listed in Appendix 13.4. In the MITT population, among patients in the pip-tazo group who were discontinued from study treatment by physician's decision, 11 of 13 patients did not complete IV treatment and none of them switched to oral therapy; and among 9 of these 13 patients who qualified to be in the efficacy (m-MITT) population, 6 patients received IV treatment for 7 to <10 days, 2 patients received 5 to <7 days and 1 patient received <5 days of IV treatment. None of those 9 patients were switched to oral therapy despite of meeting criteria for oral switch. In the mer-vab group, 4 patients discontinued treatment due to physician decision, of those, 2 patients received IV treatment for 5-7 days, 1 received 7-10 days and 1 patient received <5 days of IV treatment. None of them switched to oral therapy as was observed in the pip-tazo group. Therefore, higher rates of completion of IV treatment and switch to oral therapy in the mer-vab group should be

interpreted with caution and should not be interpreted as if mer-vab treatment is better tolerated.

Another issue found in the applicant's data was misclassification of a patient in the pip-tazo group who discontinued study drug prematurely as "efficacy failure." Detailed review of CRF and other data suggests that the patient (#300-001-518) should have been classified as "subject withdrawal". This was an 86 y/o white female, who was admitted for injury to her right wrist on (b) (6) *The patient's urine culture collected from a pre-existing catheter grew E. coli at 10^5 CFU/ml. Patient was enrolled on* (b) (6) *in the Study-505 with diagnosis of AP by criteria of fever of 38.1 C, CVA tenderness and pyuria. The patient had clinical improvement by study day 3; on* (b) (6) *patient decided to withdraw from study, as she wanted to leave the hospital, hence her EOIVT visit was performed on day 4. CRF documentation of EOIVT visit notes that her baseline sign-symptoms related to urinary tract infection was resolved; however investigator assessment of clinical outcome was incorrectly coded as "failure". This patients' correct classification should have been failure due to early withdrawal rather than lack of efficacy.*

Premature discontinuations of study treatment due to adverse events are discussed in section 8 (safety). Results are also displayed in tabular format in Appendix 13.5.

6.1.4. Analysis Population

Similar proportions of patients from the mer-vab and pip-tazo groups were eligible to be in the efficacy (m-MITT) population (192 and 182 patients in the mer-vab and pip-tazo group, respectively). All exclusions or disqualifications from the m-MITT population were due to patient having no baseline urine pathogen at $\geq 10^5$ CFU/mL.

Table below presents the number of patients valid for analyses in each of the selected populations.

Table 11 Analysis Population (Study-505)

	Treatment group		
Population	**mer-vab**	**pip-tazo**	**Total**
ITT (All Enrolled Patients)	274	276	550
MITT (Modified ITT)	272	273	545
m-MITT (Microbiologic evaluable modified ITT; Patients valid for Efficacy)	192	182	374
ME (Microbiologically Evaluable)	178	169	347

CE (Clinically Evaluable)	248	258	506
Source: Clinical Reviewers' Analysis			

Reviewer Comment: *MITT population was subset of ITT population, who received at least one dose of study drug. In this table, the reader can appreciate that the MITT population is the same population that was used for safety analysis. The m-MITT is the subset of the MITT population and is the population in which the primary outcome was evaluated.*

Table below summarize the attritions from the ITT population, and reasons for attrition.

Table 12 Primary Reasons For Microbiologic and Clinical Non-evaluability (ITT Population) - Study-505

ITT Population (all randomized patients)	**M/V (N=274) n (%)**	**P/T (N=276) n (%)**	**Total (N=550) n (%)**
MITT Population (Safety)	272 (99)	273 (99)	545 (99)
m-MITT Population (Efficacy)	192 (70)	182 (66)	374 (68)
Reason for exclusion			
No BL bacterial pathogen(s) ≥105 CFU/mL or same bacterial pathogen in concurrent blood and urine cultures	80 (29)	91 (33)	171 (31)
CE Population	248 (90)	258 (93)	506 (92)
Reason for exclusion			
Key Inclusion/Exclusion Violations [*, +]	9 (3)	2 (1)	11 (2)
No Clinical Outcome of (C/I/F) at EOIVT Unless Failure at Earlier Time Point	9 (3)	6 (2)	15 (3)
Received <80% or >120% of Expected IV Doses	3 (1)	4 (1.5)	7 (1)
Missed >1 IV Dose in First 48 Hours	3 (1)	8 (3)	11 (2)
Missed >2 Consecutive IV Doses	3 (1)	0 (0)	3 (0.6)
<6 doses for Failure or <9 doses for Cure	4 (1.5)	6 (2)	10 (2)
ME Population	178 (65)	169 (61)	347 (63)
Reason for exclusion			
No Baseline Pathogen with CFU >105 or Present in Both Blood and Urine	0 (0)	0 (0.0)	0 (0)
Key Inclusion/Exclusion Violations [*, +]	7 (4)	1 (0.5)	8 (2)
No Clinical Outcome of (C/I/F) or Microbiologic Outcome of (E/P) at EOIVT Unless Failure at Earlier time point	3 (2)	11 (6)	14 (4)
Received <80% or >120% of Expected IV Doses	3 (2)	2 (1)	5 (1)
Missed >1 IV Dose in First 48 Hours	2 (1)	4 (2)	6 (2)
Missed >2 Consecutive IV Doses	3 (2)	0 (0)	3 (1)
<6 doses for Failure or <9 doses for Cure	2 (1)	4 (2)	6 (2)

Source: Clinical Reviewers' Analysis ; and CSR Study 505
[*] Key inclusion criteria are 5 and 6; key exclusion criteria are 1, 2, 4, 5, 6, 7, 17, 21, and 22.
[+] If a patient met multiple criteria, the patient was counted only once when counting the total number of subjects excluded from the CE and ME Populations; BL: Baseline
C = Cure; CE = Clinical Evaluable; CFU = colony forming units; E = eradication; EOIVT = end of intravenous treatment; F = Failure; I = Indeterminate; ITT = Intent-to-Treat; IV = intravenous; ME = Microbiological Evaluable; MITT = Modified Intent-to-Treat; m-MITT = Microbiological Modified Intent-to-Treat; P = persistence.
* Five patients from the ITT population, 2 in mer-vab and 3 in the pip-tazo group did not receive any study drug and were not included in the MITT population.
(Patient # 300-001-502, 804-008-503 in the mer-vab group; and Patient # 112-007-505, 616-004-501, and 804-001-529 in the pip-tazo group).

Reviewer Comment*: The categories above were used to exclude patients who did not meet the protocol criteria for inclusion into the ME or CE population. Events such as death, clinical failure, and adverse events are not listed above because these were not used by the Applicant to exclude patients from microbiologic evaluability. Attrition of 80 (30%) patients in the mer-vab group and 91 (33%) patients in the pip-tazo group from MITT population resulted in m-MITT population. All of these attritions were due to no baseline bacterial pathogen(s) ≥10^5 CFU/mL or same bacterial pathogen in concurrent blood and urine cultures.*

6.1.5. Protocol Violations/Deviations

According to the Applicant, there were no major protocol violations or deviations from the study eligibility criteria that affected the efficacy or safety results. Overall, 4.4% and 2.9% of patients in the mer-vab and pip-tazo group, respectively, had a violation of an inclusion or exclusion criterion. Three patients were accidently unblinded to blinded site personnel (1 in the mer-vab and 2 in the pip-tazo group).

The Applicant reported two sites, Site 703-005 and Site 616-003, identified as having significant quality issues during the conduct of the trial. Site 703-005 enrolled 13 patients. The clinical research associate reported multiple instances of protocol noncompliance and placed the site on a corrective action plan; study personnel were retrained. The site failed to implement the required changes and, following a Quality Assurance audit by the Applicant, the site was closed for cause. Site 616-003 enrolled 6 subjects. The Clinical Research Associate reported that limited source documentation was available for data verification during multiple monitoring visits. At the time of the closeout visit, the site was still unable to provide complete source documentation. A Quality Assurance audit was conducted that confirmed findings of inadequate source documentation and lack of investigator oversight. Both sites' noncompliance was subsequently reported to the FDA, local regulatory agency, and IEC.

***Reviewers' Comment**: Efficacy and safety results were similar with and without inclusion of data from these two sites and there was no impact on the efficacy results for noninferiority.*

Besides the two sites, a larger number of patients in the mer-vab group had protocol violations in Study-505, and a subset of those patients had key inclusion or exclusion criteria (9 patients in the mer-vab group and 1 patient in the pip-tazo group) violation. Among 9 mer-vab patients with key inclusion/exclusion criteria violations, 3 patients (#642-001-501, # 642-001-508 and # 705-002-502 had no documented or suspected cUTI/AP (which was discovered later, yet subjects continued the study)). Six patients received potentially therapeutic antibacterial agent within 48 hours before randomization (# 703-005-508, # 703-005-512, # 804-005-532, # 804-005-545, # 804-009-503, and # 804-009-527). One subject # 705-002-502 had received restricted concomitant medication, i.e., another Gram negative antibacterial for a reason other than treatment failure).

There was only one patient in the pip-tazo group with key inclusion/exclusion violation (# 804-005-538). This patient received 1 dose of ciprofloxacin within 48 hours before randomization.

When looking at the outcome of patients with key protocol violations; 7 of 9 patients in the mer-vab group, and 1 patient in the pip-tazo group qualified for the m-MITT population. All of 7 patients in the mer-vab group were 'success at EOIVT' and 6 of them were 'success at TOC visit'. The patient in pip-tazo group also had overall outcome of 'success at both EOIVT, and TOC visit'.

When analysis was performed by FDA reviewers by 'excluding' patients with key violations (7 patients in mer-vab group and 1 in pip-tazo group) from the mMITT analyses, the results of efficacy analysis did not change (Reader is referred to Section 6.1.10. for sensitivity analysis).

Sensitivity analysis was also performed after excluding patients from the two sites with major protocol violations as identified by the Applicant. The results of non-inferiority assessment persisted (Reader is referred to Section 6.1.10). A table of patients with key protocol violations is listed in Appendix 13.6.

6.1.6. Demographic Characteristics

The distributions of demographic variables were similar in the two groups in both MITT and m-MITT population. Majority of patients in the mer-vab and pip-tazo groups were white, female and <65 years of age. About 14% of the patients in the mer-vab and 17% in the pip-tazo group were ≥75 years of age. Mean age was 53 years and mean BMI was approximately 26 kg/m^2 in both groups. When demographic and baseline characteristics were examined by the infection type or diagnosis group, the characteristics were similar between both treatment groups.

Table below summarizes demographic characteristics in the primary efficacy (m-MITT) population. (Demographic summary of MITT population is displayed in Appendix 13.7).

Table 13 Baseline Demographics Characteristics (m-MITT Population) - Study 505

	Study Groups MITT			Study Groups mMITT		
Demographic Parameters	Mer-vab N=272	Pip-tazo N=273	All N=545	Mer-vab N=192	Pip-tazo N=182	All N=374
Categories	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age						
< 65 years	185 (68)	170 (62)	355 (65)	130 (68)	105 (58)	235 (63)
>= 75 years	39 (14)	46 (17)	85 (16)	27 (14)	38 (21)	65 (17)
65- < 75 years	48 (18)	57 (21)	105 (19)	35 (18)	39 (21)	74 (20)
Sex/Gender						
Female	181 (66.5)	180 (66)	361 (66)	125 (65)	120 (66)	245 (65)
Male	91 (33.5)	93 (34)	184 (34)	67 (35)	62 (34)	129 (35)
Race						
White	254 (93)	252 (92)	506 (93)	178 (93)	169 (93)	347 (93)
Other	10 (4)	12 (4)	22 (4)	7 (4)	8 (4)	15 (4)
Asian	5 (2)	5 (2)	10 (2)	4 (2)	3 (2)	7 (2)
Black or African American	3 (1)	4(1)	7 (1)	3 (1.5)	2 (1)	5 (1)
Ethnicity						
Hispanic or Latino	24 (9)	19 (7)	43 (8)	14 (7)	12 (7)	26 (7)
Not Hispanic or Latino	248 (91)	254 (93)	502 (92)	178 (93)	170 (93)	348 (93)
Region						
Europe	244 (90)	243 (89)	487 (89)	173 (90)	163 (89)	336 (90)
Rest of World	16 (6)	16 (6)	32 (6)	12 (6)	10 (5)	22 (6)
North America	8 (3)	9 (3)	17 (3)	3 (2)	6 (3)	9 (2)
Asia Pacific	4 (1.5)	5 (2)	9 (2)	4 (2)	3 (2)	7 (2)
Infection Type						
Acute Pyelonephritis	161 (59)	161 (59)	322 (59)	120 (62)	101 (55)	221 (59)
cUTI with NRS	53 (19.5)	51 (19)	104 (19)	37 (19)	43 (24)	80 (21)
cUTI with RS	58 (21)	61 (22)	119 (22)	35 (18)	38 (21)	73 (19)

Source: Clinical Reviewers' Analysis; OCS Demographic analysis;
NRS= Non-removable source of infection; RS= Removable source of infection

***Reviewers' Comment**: The treatment groups as shown in the table above were well balanced in terms of baseline demographic characteristics and represent the target population for the proposed indication with the exception of race. Majority of study sites were in Europe, therefore, racial minorities are not well represented in this study, which is not congruent with the target U.S. population.*

To characterize the demographics of patients with AP as compared to cUTI, this reviewer analyzed the age and gender of patients in both subgroups by infection type. The patients with

AP were more likely to be young as compared to the cUTI patients, and majorities were females which is consistent with the target disease population in general.

6.1.7. Other Baseline Characteristics

Baseline Disease Characteristics

The types of medical history or underlying comorbidities were well balanced between the treatment groups in the m-MITT population. Most common underlying condition was hypertension (approximately 32% each group), followed by benign prostatic hyperplasia and urinary calculus (both about 14% in each group), menopause (about 10% each group), and myocardial ischemia (9% and 11% in mer-vab and pip-tazo group, respectively).

Table below summarizes baseline disease characteristics in primary efficacy population.

Table 14 Baseline Disease Demographics by Subgroup (MITT and m-MITT Population)-Study 505

	Treatment Groups MITT			***Treatment Groups m-MITT***		
	Mer-vab N-272	**Pip-tazo N=273**	**All N=545**	**Mer-vab N-192**	**Pip-tazo N=182**	**All N=374**
Categories	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
CrCl-group						
Missing	4 (1.5)	3 (1)	7 (1)	2 (1)	3 (2)	5 (1)
<30 mL/min	2 (1)	2 (1)	4 (1)	1 (0.5)	1 (0.5)	2 (0.5)
>50 mL/min	237 (87)	233 (85)	470 (86)	169 (88)	156 (86)	325 (87)
30 - 50 mL/min				20 (10)	22 (12)	42 (11)
Diabetes Status						
No	230 (85)	229 (84)	459 (84)	160 (83)	148 (81)	308 (82)
Yes	42 (15)	44 (16)	86 (16)	32 (17)	34 (19)	66 (18)
Presence of SIRS*						
No	195 (72)	183 (67)	378 (69)	137 (71)	121 (66)	258 (69)
Yes	77 (28)	90 (33)	167 (31)	55 (29)	61 (33)	116 (31)
Charlson Comorbidity Score						
<=2	129 (47)	126 (46)	255 (47)	89 (46)	77 (42)	166 (44)
>=3	143 (53)	147 (54)	290 (53)	103 (54)	105 (58)	208 (56)
Bacteremia at baseline						
No	241 (89)	243 (89)	484 (89)	175 (91)	164 (90)	339 (91)
Missing	19 (7)	15 (5.5)	34 (6)	5 (3)	3 (2)	8 (2)
Yes	12 (4)	15 (5)	27 (5)	12 (6)	15 (8)	27 (7)
Prior use of a single dose of short-acting antibacterial drugs						
No	260 (96)	264 (97)	525 (96)	186 (97)	176 (97)	362 (97)
Yes	12 (4)	9 (3)	21 (4)	6 (3)	6 (3)	12 (3)

Source: Clinical Reviewers' Analysis,

***SIRS**: Systemic Inflammatory Response Syndrome (SIRS): SIRS is defined as 2 or more of the following variables : Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F); Heart rate of more than 90 beats per minute; Respiratory rate of more than 20 breaths/min or arterial CO2 tension ($PaCO_2$) of less than 32 mm Hg; Abnormal white blood cell count (>12,000/µL or < 4,000/µL or >10% immature [band] forms

****** **Charlson Comorbidity Index Score**[43]: Used by the Applicant to assess co-morbid conditions
The Charlson Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes. Each comorbidity category has an associated weight (from 1 to 6), based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use.

Reviewers' Comment: *In terms of medical history, both treatment groups were well matched.*

Baseline renal function was similar between trial populations. Majority of patient population (about 88%) had CrCl of >50 ml/min, 10% of patients had CrCl between 30-50 ml/min and only 1 patient in each group had CrCl of <30 ml/min. In their submission, the Applicant has provided a rationale for modification of the dosing regimen in patients with severe renal impairment based on a Phase 1 study (Study-504) and population PK modeling, (b) (4) *. The dose adjustments were added as an amendment prior to start of Study-505; it is therefore, unclear why Applicant excluded patients with severe renal impairment from this Phase 3 trial. The efficacy and safety data using the modified proposed dose should have been gathered for this important subgroup. Because renal impairment is so common at baseline in the older age group particularly prone to cUTI, and pre-existing renal insufficiency is a predisposing factor for cUTI, the efficacy and safety of mer-vab is important to be evaluated in this subset of patients.*

Type-2 diabetes mellitus was present in about 16% of the patient population in Study 505. Urinary tract infections are more severe, also more often caused by resistant pathogens and carry worse outcomes in patients with type 2 diabetes mellitus.

Overall the rates of underlying comorbidities in Study 505 may be lower than in hospitalized cUTI patients in the US. An increasing comorbid condition contributes to the risk of cUTI infection, increased risk of severity, predisposition to infection with resistant bacteria and associated with poor prognosis. Charlson Comorbidity Scores were used by the Applicant as a measure of comorbidity. Each unit increase in score is associated with increased mortality. Charlson comorbidity score of ≤3 are considered low; 4 and 5 are considered as moderate, 6-7

[43] ME Charlson, P Pompei, KL Ales, CR McKenzieA new method of classifying prognostic comorbidity in longitudinal studies: Development and validationJ Chron Dis, 40 (1987), pp. 373-383

as high and ≥8 is considered very high. A correlation between scores and mortality has been shown, with scores of 0 corresponding to deaths rates of less than 0.5% and scores equal to or greater than 6 predicting death rates of ~20–25%. All scores in between demonstrate a stepped increase in mortality as comorbidity scores increase.[44]

In this trial (Study 505), baseline Charlson comorbidity index (CCI) scores were provided by the Applicant in the format of <=2 and >=3. This reviewer sent an information request to the Applicant, and subsequently individual CCI scores were provided by the Applicant (Listed in Appendix -13.8). Majority (26% in mer-vab group and 30% in pip-tazo group) of patients in Study 505 had score of "0". About 8% of patients in both groups had score of 1. Approximately 11 to 13% of patients had score of 3 to 5. About 9% in pip-tazo and 6% in mer-vab had score of 6. Rest 1-2% of patients in both groups had score of 7 to10. Figure below shows the distributions of Charlson comorbidity index (CCI) score by Infection type in Study 505.

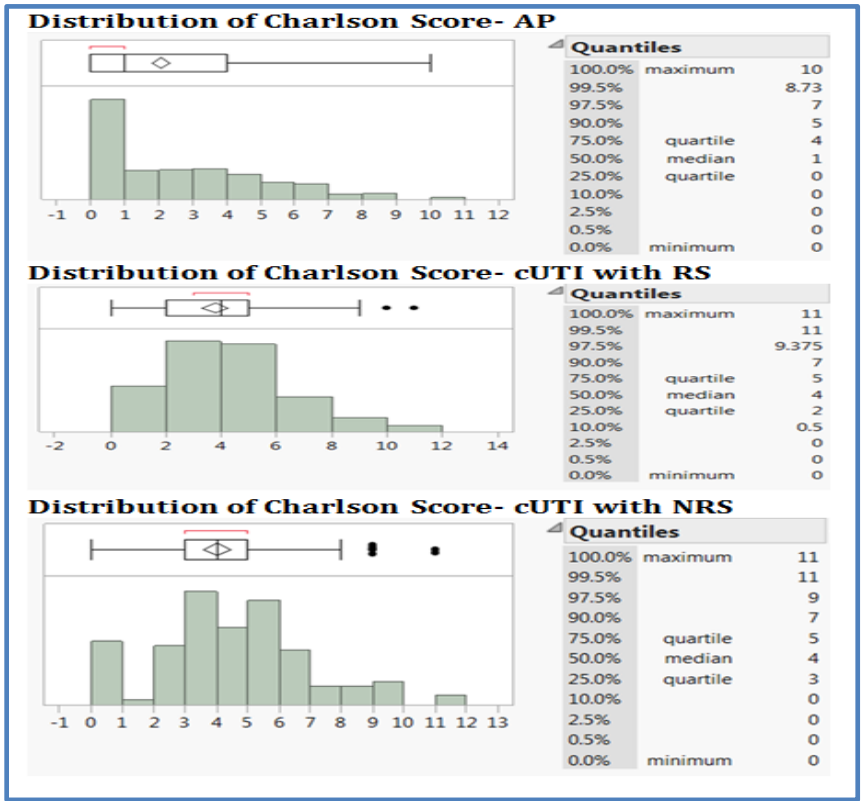


Figure 4 Distributions of Charlson Score by Infection type (MITT Population)-Study 505

[44] Jessina C. McGregor et al; Utility of the Chronic Disease Score and Charlson Comorbidity Index as Comorbidity Measures for Use in Epidemiologic Studies of Antibiotic-resistant Organisms: American Journal of Epidemiology; Vol. 161, No. 5, DOI: 10.1093/aje/kwi068

From the figure above, reader can appreciate that in addition to overall low CCI score in Study 505, comorbidity scores were 'low' in patients with AP, 'moderate' in cUTI with removable source of infection and towards 'higher side' in patients with cUTI with non-removable source of infection.

Overall, 6-8% of patients had bacteremia at baseline (6% in mer-vab and 8% in pip-tazo group). SIRS was present in 29% of patients in the mer-vab group and 33% of patients in the pip-tazo group. Overall Study 505 population may have a lesser degree of disease severity as compared to hospitalized cUTI patients in the US especially to those caused by drug resistant bacteria.

Other Baseline Clinical Characteristics

Table below summarizes the baseline Clinical characteristics of patients in m-MITT population of Study 505. Infection characteristics in the MITT, CE, and ME populations were comparable to those in the m-MITT Population.

Table 15 Baseline Clinical Characteristics of mMITT Population- Study 505

	Treatment Groups	
Characteristics	**Mer-vab N=192**	**Pip-tazo N=182**
	n (%)	n (%)
Infection Type		
Acute Pyelonephritis	120 (62)	101 (55)
cUTI with Non-Removable Source of Infection	37 (19)	43 (24)
cUTI with Removable Source of Infection	35 (18)	38 (21)
Signs/Symptoms experienced by Patient		
Pyuria	192 (100)	182 (100)
Dysuria	143 (74)	124 (68)
CV Angle tenderness	138 (72)	115 (63)
Flank Pain	132 (69)	121 (66)
Supra-pubic pain/discomfort	125 (65)	106 (58)
Urinary frequency	124 (65)	112 (61)
Urinary Urgency	102 (53)	102 (56)
Abdominal Pain	56 (29)	62 (34)
Nausea	76 (40)	66 (36)
Vomiting	20 (10)	12 (7)
Fever (Maximum Temp >38 ^{0} C)	**115 (60)**	**115 (63)**
Fever in Acute Pyelonephritis	86 (45)	78 (43)
Fever in cUTI-RS	8 (4)	18 (10)
Fever in cUTI-NRS	15 (8)	16 (9)
Mean Temperature (^{o}C) within 24 hours prior to enrollment	38.6	38.7

Source: Clinical Reviewers' Analysis and CSR, Table 16;
CV: costo-vertebral; cUTI-RS: cUTI with removable source of infection; cUTI-NRS: cUTI with non-removable source of infection;

***Reviewer Comment**: Baseline infection characteristics in the primary efficacy population were similar between the mer-vab and pip-tazo groups. Almost 100% of patients in the mer-vab and pip-tazo groups had pyuria at baseline. Next common symptom at baseline in the mer-vab and pip-tazo group was dysuria (74% and 68%, respectively), costo-vertebral angle tenderness (71% and 68%, respectively), followed by flank pain (69% and 66%, respectively), urinary frequency (65% and 61%, respectively), suprapubic pain or discomfort (65% and 58%,respectively), fever (60% and 63%, respectively), and urinary urgency (53% and 56%, respectively).*

Although not shown in the table above, it is worth mentioning that with regards to signs and symptoms based on infection type, costovertebral angle tenderness was most common symptom in patients diagnosed with AP, whereas dysuria and suprapubic discomfort was common symptom of presentation in patients with c-UTI. Most frequent signs and symptoms in patients with AP were costo-vertebral angle tenderness (89% and 86%, in the mer-vab and pip-tazo group, respectively) and flank pain (83% and 86%, in the mer-vab and pip-tazo group, respectively). Among patients with cUTI with removable source of infection, the most frequent signs and symptoms of infection in the mer-vab and pip-tazo group were supra-pubic pain or discomfort (91% and 79%, respectively) and dysuria (77% and 66%, respectively) ; whereas, in patients with cUTI with non-removable source of infection, most common presenting symptom was dysuria (92% and 79%, respectively), supra-pubic pain or discomfort (86% and 77%, respectively), and urinary frequency (86% and 81%, respectively).

Only 60% of overall patient population (without immunosuppression) had fever, and it is noteworthy that only 43-45% of patients with acute pyelonephritis were febrile on presentation, which further underscores the lower complexity of patient population in Study 505.

Table below summarizes the underlying risk factors involved in patients with cUTI in Study 505.

Table 16 Underlying Conditions Associated with cUTI with Removable and Non-removable Sources of Infections (mMITT Population) - Study 505

	m-MITT			
	cUTI with RS		cUTI with NRS	
	Mer-vab (N=35)	Pip-tazo (N=38)	Mer-vab (N=37)	Pip-tazo (N=43)
	n (%)	n (%)	n (%)	n (%)
Azotemia due to intrinsic renal disease	1 (3)	1 (3)	3 (8)	3 (7)
Indwelling urinary catheter	24 (69)	30 (79)	6 (16)	5 (12)
Neurogenic bladder with residual ≥100ml	2 (6)	3 (8)	7 (19)	13 (30)

Obstructive uropathy expected to be treated within 48hrs post randomization	14 (40)	11 (29)	18 (49)	18 (42)
Urinary retention in men due to previously diagnosed BPH	10 (29)	8 (21)	9 (24)	11 (26)
Source: Modified from Table 14.1.3.2 , Clinical Study Report; RS= Removable source of infection; NRS: Non-removable source of infection				

Reviewers' Comment*: Most frequent underlying condition or risk factor for acquiring cUTI was an indwelling urinary catheter for patients with a removable source of infection and obstructive uropathy for patients with a non-removable source of infection in both groups. Overall risk factors associated with cUTI were similar between treatment groups, except indwelling catheter and neurogenic bladder were slightly higher in the pip-tazo group as compared to mer-vab group. The number of underlying risk factors could not be compared between the AP and cUTI category, since the presence of underlying conditions was not required for AP patients.*

6.1.8. Baseline Pathogen Characteristics

Table below summarizes baseline pathogen characteristics in the efficacy (m-MITT) population. Majority of patients in both study groups had a mono-microbial infection at baseline (94% and 89%, in the mer-vab and pip-tazo group, respectively), with only 6% and 11% of patients having 2 pathogens and only 1 patient in the mer-vab group having 3 pathogens isolated.

Table 17 Baseline Pathogen in Efficacy (m-MITT) Population- Study 505

	Mer-vab (N=192)	Pip-tazo (N=182)
Number of Baseline Pathogen	n (%)	n (%)
1	180 (94)	162 (89)
=2	11 (6)	20 (11)
=3	1 (0.5)	0 (0)
Source: Clinical Study Report, Ad-hoc Table 4.1		

The pathogens recovered in urine were similar between the mer-vab and pip-tazo groups in the m-MITT Population as shown in table below.

Table 18 Common Baseline Pathogens in ≥0.5% of Patients (m-MITT Population)-Study 505

	Mer-vab (N=192)	**Pip-tazo (N=182)**
Baseline Pathogen	n (%)	n (%)
Escherichia coli	125/192 (65.1)	117/182 (64.3)
Klebsiella pneumoniae	30/192 (15.6)	28/182 (15.4)
Enterococcus faecalis	13/192 (6.8)	14/182 (7.7)

Enterobacter cloacae species complex	10/192 (5.2)	5/182 (2.7)
Proteus mirabilis	6/192 (3.1)	12/182 (6.6)
Pseudomonas aeruginosa	4*/192 (2.6)	10/182 (5.5)
Staphylococcus saprophyticus	5/192 (2.6)	0/182 (0.0)
Citrobacter freundii species complex	2/192 (1.0)	3/182 (1.6)
Morganella morganii	1/192 (0.5)	3/182 (1.6)
Acinetobacter baumannii-calcoaceticus Sp. complex	1/192 (0.5)	2/182 (1.1)
Klebsiella oxytoca	2/192 (1.0)	1/182 (0.5)
Citrobacter koseri	1/192 (0.5)	1/182 (0.5)
Proteus vulgaris	1/192 (0.5)	1/182 (0.5)
Providencia rettgeri	0/192 (0.0)	2/182 (1.1)

Source: Applicant's Table 17, CSR (Modified version)
*The Applicant notes 5 patients whereas Clinical Reviewers' analysis has yielded **4** patients (# 076-004-501, 100-007-502, 804-002-512, and 804-007-505) with *Pseudomonas aeruginosa* in the mer-vab group and 10 patients in the pip-tazo group.

***Reviewers' Comment**: E. coli was the most common pathogen in urine isolated in more than 60% of patients in both study groups. K. pneumoniae was isolated in about 15% of patients in both study groups.*

Table below displays the number of patients with Resistant Bacteria in Study-505

Table 19 Number of Patients with Resistant Bacteria (m-MITT Population) - Study 505

Baseline Pathogen	mer-vab (N=192)	pip-tazo (N=182)
	n (%)	n (%)
Escherichia coli	124	115
Meropenem-Resistant	0	0
Piperacillin/tazobactam-Resistant	7	6
Klebsiella pneumoniae	30	27
Meropenem-Resistant	1 (MIC: 64)	2
Piperacillin/tazobactam-Resistant	15	9
Proteus mirabilis	6	12
Meropenem-Resistant	0	0
Piperacillin/tazobactam-Resistant	0	0
Pseudomonas aeruginosa	4	10
Meropenem-Resistant	2 (MICs: 16, and >64)	4
Piperacillin/tazobactam-Resistant	1	4

Source: Clinical Reviewers' Analysis with Reference to Applicant's Table 18, CSR 505

Of note: Meropenem resistant organisms were susceptible to meropenem-vaborbactam. Meropenem Resistant is inked in 'red'; Piperacillin/tazobactam resistant is inked in 'blue'

***Reviewers' Comment**: It is noteworthy that there were a disproportionately higher number of patients in the pip-tazo group with piperacillin/tazobactam resistant pathogens (marked in blue) as compared to meropenem resistant pathogens in the mer-vab group (marked in red). Pip-tazo resistant pathogens were also higher in the mer-vab group. This could be partially explained by the fact that piperacillin/tazobactam is approved for treatment of cUTIs in Europe and other parts of the world, and most patients were likely exposed to this drug resulting in selection of resistance in the infecting bacteria.*

Due to lack of meropenem resistant pathogens in this study (apart from one patient with K. pneumoniae and 2 patients with Pseudomonas aeruginosa infection), it is difficult to ascertain the contribution of vaborbactam in the microbiological efficacy of meropenem-vaborbactam in Study 505.

Table below shows list of pathogens isolated in Urine by Infection type at baseline in patients valid for efficacy (m-MITT).

Table 20 Pathogens Isolated in Urine by Infection Type at Baseline- Study 505 (m-MITT)

	Infection Type (m-MITT)-Study 505					
	AP		**c-UTI with Removable Source**		**c-UTI with Non-removable Source**	
	Mer-vab n=120	Pip-tazo n=101	Mer-vab n=35	Pip-tazo n=38	Mer-vab n=37	Pip-tazo n-43
Escherichia coli	*92*	*78*	*16*	*19*	*17*	*20*
Klebsiella pneumoniae	*15*	*9*	*9*	*8*	*6*	*11*
Enterococcus faecalis	*1*	*8*	*4*	*6*	*8*	*0*
Enterobacter cloacae sp complex	*5*	2	*3*	0	*2*	3
Pseudomonas aeruginosa	1*	2	3	4	0	4
Proteus mirabilis	1	3	2	5	0	0
Enterococcus faecium	0	0	0	0	0	1
Staphylococcus saprophyticus	5	0	0	0	0	0
Acinetobacter baumanii	1	1	0	1	0	0
Citrobacter koseri	1	1	0	0	0	0
Citrobacter freundii sp	1	0	0	2	1	1
Pseudomonas putida	1	0	0	0	0	0

	Infection Type (m-MITT)-Study 505					
	AP		**c-UTI with Removable Source**		**c-UTI with Non-removable Source**	
	Mer-vab n=120	Pip-tazo n=101	Mer-vab n=35	Pip-tazo n=38	Mer-vab n=37	Pip-tazo n-43
Staphylococcus aureus	0	1	0	0	0	0
Morganella morganii	0	0	1	2	0	1
Klebsiella oxytoca	0	0	1	0	1	1
Proteus vulgaris	0	0	1	0	0	1
Providencia rettgeri	0	0	0	1	0	1
Providencia stuartii	0	0	1	0	0	0
Unspeciated enterococcus	0	0	1	0	0	0
Serratia marcescens	0	0	0	0	0	1
Source: CSR 505, Ad Hoc Table 4.1 *Applicant presented 2 subjects.*						

***Reviewers' Comment**: The bacterial spectrum in this study consisted of higher proportion of E. coli overall. In terms of pathogens by infection type, proportion of E. coli was higher in patients with AP (approximately 77% in both groups), whereas, proportion K. pneumoniae was higher in patients with cUTI (26% and 21% in the mer-vab and pip-tazo group, respectively, with removable source of infection; 16% and 26% in the mer-vab and pip-tazo group respectively, with non-removable source of infection).*

Table below displays outcomes in patients infected with *Pseudomonas aeruginosa* by meropenem MIC and susceptibility, the m-MITT population, Study-505.

Table 21 Outcomes in Patients with *Pseudomonas aeruginosa* by Meropenem MIC and Susceptibility (m-MITT) - Study 505

Subject-ID	Susceptibility	Mero-MIC	Tx Group	*MRTOC*	*CRTOC*	*ORTOC*
REMPEX-505-076-004-501	SUSCEPTIBLE	<=0.5	Mer-Vab	*Erad*	*Cure*	*Success*
REMPEX-505-100-007-502	SUSCEPTIBLE	<=0.5	Mer-Vab	*Erad*	*Cure*	*Success*
REMPEX-505-804-002-512*	RESISTANT	>64	Mer-Vab	*Erad*	*Cure*	*Success*
REMPEX-505-804-007-505	RESISTANT	16	Mer-Vab	*Erad*	*Cure*	*Success*
REMPEX-505-112-004-502	RESISTANT	32	Pip-Tazo	***Recurr****	*Failure*	*Failure*
REMPEX-505-112-004-507	RESISTANT	16	Pip-Tazo	*Erad*	*Cure*	*Success*
REMPEX-505-300-001-503	SUSCEPTIBLE	<=0.5	Pip-Tazo	*Indeter*	*N-A*	*Indeter*
REMPEX-505-300-004-501	SUSCEPTIBLE	1	Pip-Tazo	*Erad*	*Cure*	*Success*
REMPEX-505-642-002-505	RESISTANT	32	Pip-Tazo	*Recur*	*Cure*	*Failure*

Subject-ID	Susceptibility	Mero-MIC	Tx Group	*MRTOC*	*CRTOC*	*ORTOC*
REMPEX-505-642-002-506	RESISTANT	64	Pip-Tazo	***Persist***	*Failure*	*Failure*
REMPEX-505-703-005-513	SUSCEPTIBLE	<=0.5	Pip-Tazo	*Eradi*	*Cure*	*Success*
REMPEX-505-804-002-532	SUSCEPTIBLE	2	Pip-Tazo	*Eradi*	*Cure*	*Success*
REMPEX-505-804-005-541	SUSCEPTIBLE	<=0.5	Pip-Tazo	*Recurr*	*Cure*	*Failure*
REMPEX-505-804-005-546	SUSCEPTIBLE	<=0.5	Pip-Tazo	*Recur*	*Cure*	*Failure*
Source: Clinical Reviewers' Analysis *This subject had 2 isolates of *P. aeruginosa* **Recurrence and persistence occurred at EOIVT (Day-5)						

Reviewers' Comment: (b) (4)

[redacted]

[redacted].

6.1.9. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Exposure to Study drugs and Treatment Compliance

The planned total duration of therapy (IV and oral) was 10 days, excepting that patients with concurrent bacteremia could receive 14 days of therapy. After at least 15 doses (5 days) of IV therapy, patients could be switched to oral levofloxacin (500 mg, every 24 hours) or other selected oral alternatives if infecting bacteria were resistant to levofloxacin, based on pre-specified criteria as mentioned in this review before.

The mean duration of IV therapy in the m-MITT population was about 8 days in both groups. About 99% of patients in each group were ≥80% compliant with IV therapy. Approximately 61% of patients in the mer-vab and 52% in the pip-tazo group switched to oral therapy. For patients who switched to oral therapy, mean duration of oral therapy was about 4.5 days in both groups and compliance to oral therapy was 99% and 100% in the mer-vab and pip-tazo group, respectively.

Levofloxacin was the most frequently used antibacterial drug for oral step-down therapy (93% and 94% in the mer-vab and pip-tazo group, respectively). About 10% of patients in both groups were switched to oral step-down therapy with levofloxacin despite having a levofloxacin-resistant pathogen at baseline. Similar results for study drug exposure were seen in the MITT, CE, and ME Populations.

Table below displays the results of treatment exposure and compliance in Study-505

Table 22 Treatment Exposure and Compliance in Efficacy population- Study 505

	m-MITT (Efficacy) Population	
	Mer-vab N=192	**Pip-tazo N=182**
IV Tx Exposure (days)		
<5 days	5 (3)	8 (4)
>=5 - <7 days	68 (35)	64 (35)
>=7 - <10 days	53 (28)	40 (22)
10-11 days	64 (33)	68 (37)
>11 days	2 (1)	2 (1)
Mean duration of IV Tx	8.1	8.2
Compliance with IV Tx		
<80%	1 (0.5)	2 (1)
>=80%	190 (99)	180 (99)
Patients switched to Oral Tx	117 (61)	94 (52)
Time to Oral Switch		
>10 days	1 (0.5)	0 (0)
5 - 10 days	116 (60)	94 (52)
Oral Tx Exposure (days)		
<1 day	75 (39)	88 (48)
1 day to 4 days	41 (21)	29 (16)
5 days to 6 days	74 (38.5)	65 (36)
>6 days	2 (1)	0 (0)
Mean Duration of Oral Tx	4.5	4.5
Compliance with Oral tx		
>=80%	116/117 (99)	94/94 (100)
Subjects Who Received Oral Step-Down Therapy	116 (60)	94 (52)
Bactrim	5 (4)	1 (1)
cefixime	3 (3)	3 (3)
Levofloxacin	109 (93)	88 (94)
Other	1 (0.9)	2 (2)
Resistant to Levofloxacin		
Overall	19/192 (10)	15/182 (8)
Pyelonephritis	8/120 (7)	8/101 (8)
c-UTI with removable source of infection	5/35 (14)	5/38 (13)
c-UTI with non-removable source of infection	6/37 (16)	2/43 (5)

Source: Combined ADSL Clinical Reviewers' Analysis and CSR

***Reviewers' Comment**: Non-completion of study treatment was due to physician decisions, patient withdrawals from study, adverse events, and other less common reasons. In general, treatment compliance was balanced between the two treatment groups.*

It appears from the table above that higher proportion of patients in the mer-vab group switched to oral therapy as compared to the pip-tazo group. However, this should not be implied as mer-vab treatment was more effective at facilitating the transition to oral therapy as compared to pip-tazo treatment, because, as discussed in section 6.1.2.1, about twice the number of patients in the pip-tazo group as compared to the mer-vab group was prematurely discontinued from IV study drug due to physicians' decision and none of those patients were given oral therapy on discharge.

Prior Medications

A similar proportion of patients in the mer-vab and pip-tazo group (51[27%] and 47 [26%], received other prior medications for their underlying chronic illnesses.

Prior Antibacterial drugs

Table below shows the use of prior antibacterial drugs in study 505. The results for prior antibacterial use was similar in MITT, CE and ME population.

Table 23 Prior Antibacterial Use in Study-505 (m-MITT population)

	m-MITT Population	
	mer-vab (N=192)	**pip-tazo (N=182)**
	n (%)	n (%)
Prior short acting antibacterials within 24 hours of enrollment	6 (3.1)	6 (3.3)
Prior Systemic Antibacterials for Current Episode of cUTI	2 (1.0)	4* (2.0)
Prior Systemic Antibacterials for Another Indication	1 (0.5)	1 (0.5)

Source: Applicant's Table 14.1.6.1.1,2,3, CSR study 505

**2 patients received piperacillin/tazobactam (# 840-017-501; #300-001-514) and 1 patient received piperacillin (#724-009-506)*

***Reviewers' Comment**: Prior antibacterial drugs were the medications used by patients within 2 weeks of study enrollment and discontinued before the first dose of study drug. The use of prior antibacterial drugs for systemic use was low in Study 505, and was similar in both treatment groups. However, there were 4 patients in the pip-tazo as compared to 2 patients in mer-vab group with a history of prior antibacterial use for current episode of cUTI. Of 4 patients with a*

history of prior antibacterial drug use, 2 patients received piperacillin/tazobactam (# 840-017-501; #300-001-514) and 1 patient received piperacillin (#724-009-506).

Most common antibacterials used in more than 1% of patients in the mer-vab group were cefuroxime; gentamicin, ciprofloxacin, amoxicillin-clavulanate, and nitrofurantoin; whereas in the pip-tazo group amikacin, ciprofloxacin, and ceftriaxone were most commonly used. The presence of fewer numbers of patients with a history of prior antibacterial drugs likely reflects that majority of patients in this trial were less treatment experienced, and had generally less severe disease.

The study protocol allowed a single dose of short acting antibacterial treatment within 48 hours of enrollment period. Overall about 4% of patients in mer-vab group and 3% of patients in pip-tazo group received one dose of a short acting antibiotic within 24 hours of enrollment in valid for efficacy population (excluding patients who had protocol violations). The short-acting antibacterials taken by more than one patient in either group were amoxicillin-clavulanate, gentamicin, and cefotaxime.

Concomitant Therapy

With respect to concomitant therapy, patients were permitted to continue non-antibacterial therapies other than probenacid, valproic acid, vecuronium, and/or methotrexate. The protocol did not allow additional or adjunctive antibacterial therapy for cUTI, with the exceptions of Gram-positive only coverage (e.g., vancomycin, daptomycin, or linezolid) as deemed necessary by the investigator, or for local care of superficial wounds.

The majority of subjects in the mer-vab and pip-tazo group (135 [70%] and 136 [75%], respectively) in the MITT Population received non-bacterial concomitant medications that were started either on or after the first infusion of study drug. The types of concomitant medications were balanced between the treatment groups. The most frequent (>5% of patients in either group) concomitant medications used were paracetamol (14.7% and 12.1%), ketorolac (7% and 8%), drotaverine (7.3% and 6.6%), and omeprazole (5% and 7%).

6.1.10. Efficacy Results

6.1.10.1. Efficacy Results- Primary and Secondary Endpoints

Primary Endpoint

Noninferiority for the primary efficacy endpoint, which was overall success at EOIVT visit in the m-MITT Population, was met in this trial.

The table below displays results for the primary efficacy analysis of Overall Response at the EOIV visit in the m-MITT population.

Overall Response at EOIVT

Table 24 Applicant's Analysis of Overall Response at EOIV (m-MITT population)-Study 505

Overall Response	Mer-vab	Pip-tazo	Difference	95% CI
Success	189/192 (98.4%)	171/182 (94.0%)	4.5%	0.7% to 9.1%
Failure	2/192 (1.0%)	8/182 (4.4%)		
Indeterminate	1/192 (0.5%)	3/182 (1.6%)		
Source: Clinical Study Report 505, Table 14.2.1.3.				

This trial was designed to evaluate noninferiority with a pre-specified non-noninferiority margin of -15%. There was a statistically significant difference between the mer-vab success rate of 98.4% and the pip-tazo success rate of 94.0% with a difference in success rates of 4.5%, and the lower confidence limit of 0.7% for the difference exceeded zero. Based on this analysis,, mer-vab appeared to be numerically superior to pip-tazo at EOIVT visit.

***Reviewers' Comment**: The overall success rates at EOIVT were high in both groups. Apart from 3 isolates, all pathogens were meropenem sensitive. As discussed earlier in Analysis of condition section of this review, having an infection with resistant pathogen itself is cause of poor outcome and excess mortality.*

Of note, all the failures at EOIVT in the mer-vab group (3 patients) were due to adverse events (infusion related allergic reaction) which were related to study drug. Half of the failures at EOIVT in the pip-tazo group (4 of 8 patients) had adverse events, of which 2 were related to hypersensitivity due to study drug, and 2 deaths according to the investigator assessment were not related to study drug (#300-001-514 died of septic shock on D-3; and # 804-008-505 was clinical cure at D-5 , EOIVT however, had an incidental diagnosis of colon cancer); One patient withdrew consent from the study as they did not want to undergo study procedures, and remaining 3 patients had complicated UTI with pip-tazo resistant baseline pathogens (2 patients with Pseudomonas aeruginosa, and 1 patient with K. pneumoniae), with prior therapy failures. These 3 patients were clinical cure or improvement, however were considered failure due to microbiologic persistence or recurrence.

FDA Reviewer's sensitivity analysis for Overall Response at EOIV in Study 505

The most conservative method for estimating study drug treatment effect was to consider indeterminate or missing values to be failures in the mer-vab group but success in the pip-tazo group, because any other method of imputation will give results more favorable to mer-vab. The table below shows the results of sensitivity analysis.

Table 25 FDA Reviewer's Sensitivity Analysis of Indeterminate Overall Response at EOIV in Study 505 (m-MITT population)

Overall Response	Mer-vab	Pip-tazo	Difference	95% CI
Success	189/192 (98.4%)	174/182 (95.6%)	2.8%	-0.7% to 7.1%
Failure	3/192 (1.6%)	8/182 (4.4%)		
Source: FDA Statistical Reviewer , Daniel Rubin, Ph.D.				

***Reviewers' Comment**: Table above is a post-hoc analysis of indeterminate data, where FDA statistical reviewers' analysis was conservative for the treatment effect. The lower confidence limit for the difference in success rates still fell within pre-specified 15% non-inferiority margin. Although notably, the lower confidence limit of -0.7% for the treatment effect no longer would meet superiority criteria. The changes from this analysis do not significantly affect the study results or its interpretation. These analyses support the conclusion that mer-vab is non-inferior to pip-tazo for the treatment of cUTI/AP.*

Table below displays the results of sensitivity analysis after excluding the patients from two sites with major protocol violations.

Table 26 Sensitivity analysis of Overall Response at EOIV after Excluding Patients from the Applicant Identified Two sites with Major Protocol Violations - Study 505 (m-MITT Population)

Overall Response	Mer-vab	Pip-tazo	Difference	95% CI
Success	183/186 (98.4)	165/175 (94.3)	4.1	-0.3% to 8.8%
Failure	2/186 (1.1%)	8/175 (4.6%)		

Indeterminate	1/186 (0.5%)	2/175 (1.1%)		
Source: CSR, Table 14.2.1.2a Note: Indeterminate were considered failures				

***Reviewers' Comment**: The Applicant also conducted a sensitivity analysis, excluding data from two sites (Sites 616-003 and 703-005), which had major protocol violations, and the overall results remained unchanged. Thus, protocol violations in these two sites do not affect efficacy conclusions for study 505. . Due to the relatively small number of subjects from the affected study sites and the insensitivity of the main trial conclusions to these subjects, the rest of analyses in this review did not exclude these study sites. Reader is referred to Appendix-13.9 for table summarizing outcome of patients at sites 703-005 and 616-002.*

As discussed in section 6.1.5, there were 7 patients in the mer-vab group and 1 patient in the pip-tazo group with key protocol violations (violations of key inclusion/exclusion criteria). Table below shows the FDA sensitivity analysis after excluding patients who were identified to have key protocol violations in Study 505.

Table 27 FDA Sensitivity Analysis after excluding patients with 'Key protocol Violations' – Study 505 (m-MITT population)

Overall Response	Mer-vab	Pip-tazo	Difference	95% CI
Success	182/185 (98.4%)	170/181 (93.9%)	4.5	0.6, 0.9
Failure	2/186 (1.1%)	8/175 (4.6%)		
Indeterminate	1*/186 (0.5%)	2/175 (1.1%)		
Source: FDA Statistical Reviewer *AE of generalized body tremor leading to study drug discontinuation on D-3.				

***Reviewers' Comment**: The difference in success rates is 4.5%, with a 95% confidence interval for the difference from 0.6% to 9.1%. Therefore, this analysis does not change the interpretation of original results.*

Clinical Reviewers' Evaluation of Patients with Overall Response of 'Failure' at EOIVT visit in the mer-vab and pip-tazo group

Overall Response - Failure at EOIVT (mer-vab group):

Both failures in the mer-vab group were due to adverse events of infusion related reaction. Both were related to study drug. Additionally, one indeterminate outcome in the mer-vab

group also had an adverse reaction of generalized tremor on Study day 3, leading to study drug discontinuation.

Overall Response-Failure at EOIVT (pip-tazo group):

In the pip-tazo group, 4 of 8 patients had failure due to AEs. One patient withdrew from study since they did not want to undergo required study procedures and were unwilling to stay in hospital; and the rest 3 patients had infection with pip-tazo resistant baseline pathogen (Table 28).

Table 28 Reasons for Overall Response of Failure in Piperacillin-Tazobactam Group

#	SUBJECT-ID	Failure Reason	IFN Type	CR EOIVT	MR EOIVT	BL Pathogen	MIC P/T	CLSI
1	112-004-502	Pip-tazo Resistant	cUTI/NR	Improv	Recur	*P. aeruginosa*	>64	R
2	642-002-506	Pip-tazo Resistant	cUTI/R	Cure	Persist	*P. Aeruginosa*	64	R
3	642-001-506	Pip-tazo Resistant	cUTI/NR	Improv	Recur	*K. pneumoniae*	>64*/4	R
4	300-001-518	Withdrawal after 1 dose	AP	Failure	Indeter	*E. coli*	4	S
5	300-001-514	AE (Not Related) Septic Shock-D2	AP	Failure	Indeter	*E. coli*	2	S
6	804-008-505	AE (Not Related)**	AP	Failure*	Erad	*E.faecalis*	2	S
7	158-001-508	AE (Possibly Related) Febrile Rash –D 6	AP	Failure	Indeter	*E. coli*	2	S
8	642-003-501	AE (Possibly Related) Hypersensitivity-D3	cUTI/R	Failure	Indeter	*E. coli*	2	S

Source: CLINICAL REVIEWERS' ANALYSIS ;
D= study day; CLSI= CLSI sensitivity analysis for FDA; AE= adverse event; BL=baseline; Improv= improvement; Persist= persistence; Recur= recurrence; CR-EOIVT: clinical response at EOIVT; MR-EOIVT: microbiologic response at EOIVT

**Two MICs and two CLSI sensitivity interpretations were given for this patient in the Applicant data set. The microbiology results for EOIVT and TOC were available in the data set. Baseline pathogen urinary isolate primer # was not provided.*

*** Patient met the criteria for clinical cure, and had microbiologic eradication on day-5 (EOIVT) visit, however, he had an accidental diagnosis of cecal cancer during renal ultrasound as routine procedure later the same day, and therefore he was assigned as "failure".*

Clinical and Microbiologic Response at EOIVT visit

Overall Response at EOIVT was a composite endpoint requiring both clinical and microbiological outcomes to be successful. Table 29 and Table 30, shows analysis of clinical and microbiologic outcomes separately at EOIVT visit in the efficacy population.

Table 29 Clinical Outcome at EOIVT visit (m-MITT Population) - Study 505

Clinical Outcome	Mer-vab	Pip-tazo	Difference	95% CI
Cure	156/192 (81.2%)	144/182 (79.1%)	2.1%	-6.0% to 10.3%
Improvement	33/192 (17.2%)	30/182 (16.5%)		
Failure	2/192 (1.0%)	5/182 (2.7%)		
Indeterminate	0/192 (0.0%)	1/182 (0.5%)		
Not Assessed	1/192 (0.5%)	2/182 (1.1%)		
Source : CSR, Table 14.2.2.1				

***Reviewers' Comment**: For clinical outcome at EOIVT, success rate remained numerically higher for the mer-vab group and met pre-specified non inferiority margin. The outcomes of "indeterminate" and "not assessed" in both groups were explored further by this clinical reviewer. The patient listed as "not assessed" in the mer-vab group (# 804-008-506), was enrolled with diagnosis of AP. This patient experienced an AE after receiving 1 dose of study drug, and therefore, should have been categorized as "failure". Similarly 2 patients with "not assessed" outcome in the pip-tazo should have been categorized as "failure" (patient # 703-005-509 was 81 year old female enrolled with diagnosis of AP, developed an AE after 1 dose of study drug; and, patient # 840-014-503 was enrolled with cUTI, and this patient withdrew consent after receiving 2 doses of study drug, because patient "did not want to be bothered with required study related procedures").*

The patient with indeterminate outcome in pip-tazo group (patient # 724-009-506) was a 39 year old female with AP. She had an episode of lacunar infarct (left hemihypostesia) after receiving 2 doses of study drug. Notably, indeterminate outcomes were not counted toward cure, so regardless of categorization of these outcomes as indeterminate or failure, success rates in study 505 at EOIVT remain unchanged.

Table 30 Microbiological Outcome at EOIVT (m-MITT Population) - Study 505

Microbiologic Outcome	Mer-vab	Pip-tazo	Difference	95% CI
Eradication	188/192 (97.9%)	168/182 (92.3%)	5.6%	1.4% to 10.7%
Persistence	0/192 (0.0%)	1/182 (0.5%)		
Recurrence	0/192 (0.0%)	2/182 (1.1%)		
Indeterminate	4/192 (2.1%)	**11**/182 (6%)		
Source : CSR, Table 14.2.2.1 (Results verified by FDA reviewers)				

***Reviewers' Comment**: The microbiologic eradication rates at EOIVT were higher in the mer-vab group compared to the pip-tazo group, however, it should be noted that there were disproportionately higher (almost 3 times higher) number of patients in pip-tazo group with "Indeterminate" microbiologic outcome.*

Microbiologic outcome of persistence or recurrence were reported for 3 patients at EOIVT in Study 505. All were reported in the pip-tazo group (1 case of persistence and 2 case of recurrence; all these patients had recent history of prior therapy for cUTI). All three patients were diagnosed with cUTI with non-removable source of infection. A brief summary of CRF review is listed below for 3 cases.

Patient # 642-002-506 (cUTI with non- removable source of infection)

This patient was a 65-year-old female, who had a history of hospitalization 1.5 months ago with the diagnosis of cUTI with an underlying non removable source of infection. Patient was found to have nephrolithiasis and had a right ureteral stent placement. Patient was noted to have urinary stent replacement on the day before screening (b) (6)). Screening day was (b) (6). On screening day, patients' temperature was 36^{o} C (afebrile), physical examination was documented in CRF as "normal". Sign/Symptoms were recorded as positive for nausea, urinary urgency, flank pain and suprapubic pain. Urine culture on Day 1 was positive for Pseudomonas aeruginosa at 10^{5} CFU/ml. Patient was randomized to the pip-tazo group on (b) (6) On Day3, urinary urgency and suprapubic discomfort continued. Day 3 culture remained positive. Clinical Outcome was "Improvement". All sign/symptoms and physical examination were normal at Day 4-10 per CRF documentation, except for urgency, which continued. EOIVT visit was performed on Day 10 (b) (6)), when clinical outcome was assessed as "Cure"; and microbiologic outcome of "persistence" due to continued positive urine culture for Pseudomonas aeruginosa at 10^{4} CFU/ml. At TOC (b) (6)), patient had continuing urinary urgency and frequency with relapsed suprapubic tenderness. He was assessed as overall response of "failure" and was discharged home on oral therapy (cefixime).

Of note, this patient was infected with baseline pathogen resistant to piperacillin-tazobactam with MIC of >64. Therefore, it is not unexpected for this patient to have persistent bacteriuria and microbiologic persistence. However, patient responded well clinically.

Patient # 642-001-506 (cUTI with non- removable source of infection)

This patient was a 79- year- old female with chronic kidney disease, and a long history of pyeloureteral junction stenosis, right kidney stones and right pyelolithotomy along with other comorbid conditions. Two months prior to enrollment in the study, patient had right kidney extracorporeal shock wave lithotripsy for recurrent stone. One month prior to enrollment patient had a right retrograde ureterorenoscopy and right ureteral catheter placement (b) (6)).The patient was screened and enrolled in Study 505 on (b) (6) with diagnosis of cUTI and had a replacement of right ureteral stent. Patient was afebrile with new onset of nausea, urgency, dysuria, supra-pubic pain and costovertebral angle tenderness. Urine culture

on the day of screening was positive for Klebsiella pneumoniae (MIC of 4). The patients' clinical sign/symptoms noted in CRF as either resolved or decreased on Day 3 to Day 8. EOIVT visit was performed on Day 8. Patient was assessed as clinical outcome of improvement, with microbiologic outcome of "recurrence".

Patient # 112-004-502 (cUTI with non- removable source of infection)

This patient was a 25–year-old female who was randomized on (b) (6) for c-UTI with non-removable source of infection. The patient had a recent history of nephrolithotomy and nephrostomy on 8/7/15; with subsequent left ureteral stent placement on (b) (6), and pyeloplasty with decapsulation of left kidney on (b) (6). Patient was being treated for cUTI with colistin and fluconazole prior to enrollment in study 505. On September 28, 2015 while the patient was completing treatment with colistin, a urine culture was taken which tested positive for Pseudomonas aeruginosa on (b) (6) (MIC of 64). The patient was randomized to the pip-tazo group on the same day (b) (6). The patient had an EOIVT visit on Study day 10 (b) (6), when the investigator assessed clinical outcome as "improvement" and microbiologic outcome was noted as "recurrence". On Study Day 16 (b) (6)), the patient presented at the hospital with shivers, deterioration in her health with aching back pain and a body temperature of 39ºC and was hospitalized on Study Day 16 in the urology department. The subject's kidney ultrasonography on Study Day 16 revealed stones in both kidneys and several calculi up to 13 mm in the left utero-pelvic junction. Subject was treated with cefoperazone/sulbactam, and fluconazole. TOC visit was performed on (b) (6) and was assessed as overall response of "failure". On study day 23 (b) (6) the patient was reported to have improvement in clinical condition and was discharged from the hospital.

Table below displays baseline pathogen susceptibility, MICs and Clinical response at EOIVT visit for patients with Microbiologic outcome of "Indeterminate" in the pip-tazo and mer-vab groups.

Table 31 MICs, Susceptibility, Baseline Pathogen Information for patients with Microbiological Outcomes "Indeterminate" at EOIVT (m-MITT population)-505

No.	USUBJID	BL Pathogens	MIC	Susc	IFN-Type	CREOIVT
Micro Outcome Indeterminate at EOIVT in pip-tazo group						
1	505-112-002-514	*E. COLI*	32	S	AP	Cure
2	505-158-001-508	*E. COLI*	2	S	AP	Failure
3	505-300-001-514	*E. COLI*	2	S	AP	Failure
4	505-300-001-518	*E. COLI*	4	S	AP	Failure
5	505-642-003-501	*E. COLI*	2	S	cUTI wRS	Failure

No.	USUBJID	BL Pathogens	MIC	Susc	IFN-Type	CREOIVT
6	505-703-005-501	*E. COLI*	32	S	cUTI wRS	Cure
7	505-703-005-509	*E. COLI*	1	S	AP	Not Assessed
8	505-724-009-506	*E. COLI*	16	S	AP	Indeterminate
9	505-804-003-507	*E. COLI*	2	S	AP	Cure
10	505-840-014-503	*E. COLI*	32		cUTI wRS	Not Assessed
11	505-804-007-518	*K. PNEUMONIAE*	>64	R	cUTI wRS	Cure
Micro Outcome Indeterminate at EOIVT in mer-vab group						
1	505-112-004-508	*E.COLI*	<=0.5	S	AP	Failure
2	505-604-004-502	*K. PNEUMONIAE*	<=0.5	S	AP	Failure
3	505-616-006-501	K. OXYTOCA	<=0.5	S	cUTI wNRS	Cure
4	505-804-008-506	E. COLI	<=0.5	S	AP	Not Assessed
Source: Clinical Reviewers' Analysis Susc= susceptibility; wRS= with removable source of infection; wNRS= with non-removable source of infection						

***Reviewers' Comment**: The baseline pathogen for all microbiologic 'indeterminate' outcome in pip-tazo group were E. coli, except for one, which was Klebsiella pneumoniae with MIC >64. Four of 11 indeterminate had clinical outcome of Cure, including 2 cases of microbiologic recurrence, and 1 case of microbiologic persistence who had achieved outcome of 'Improvement' or 'Cure' clinically. Three patients with microbiologic 'indeterminate' outcomes were 'not assessed' clinically. Reason for non-assessment was not provided in CRF. In mer-vab group, all 4 cases of microbiologic indeterminate outcome had infection with susceptible strain of E. coli. Two of those 4 cases had clinical outcome of failure; 1 patient was 'not assessed' clinically and remaining 1 patient had clinical outcome of cure.*

Overall Response at the TOC visit

The table below shows results for Overall Response at the TOC visit scheduled for Day 15-19. Success rates for this endpoint were lower in both treatment groups as compared to response at EOIV; however, the success rate was numerically higher for the mer-vab group than the pip-tazo group.

Table 32 Analysis of Overall Response at TOC (m-MITT population)-Study 505

Overall Response	Mer-vab	Pip-tazo	Difference	95% CI
Success	143/192 (74.5%)	128/182 (70.3%)	4.1%	-4.9 to 13.2
Failure	41/192 (21.4%)	40/182 (22.0%)		
Indeterminate	8/192 (4.2%)	**14**/182 (7.7%)		
Source: Table 14.2.1.6. Clinical Study Report 505				

***Reviewers' Comment**: According to the current Agency guidance document on developing antibacterial drugs for the treatment of cUTI (2015), when a drug only has an intravenous formulation, the trial should use co-primary endpoints at time points defined at the expected end of intravenous therapy and after expected completion of both intravenous and oral therapy, which is test of cure (TOC) visit. The reason to make both assessments is that the results at the EOIV visit are not affected by oral therapy, while sustained response after a period of observation after completion of treatment is considered more clinically meaningful. Study 505 defined only a single primary endpoint at the EOIV visit because the trial began before the FDA guidance was finalized.*

As displayed in the table above, success rates at TOC were lower in both treatment groups as compared to EOIV. However, the success rate was numerically slightly higher for the mer-vab group as compared to pip-tazo group, meeting non-inferiority. Failure rates were similar between the mer-vab and pip-tazo group at TOC and majority of the failures at TOC was due to recurrence of baseline pathogen.

Table below presents FDA Reviewers' Sensitivity Analysis to Evaluate Overall Response at TOC after excluding patients who had key protocol violations.

Table 33 FDA Reviewers' Sensitivity Analysis to Evaluate Overall Response at TOC after Excluding Patients with Violation of Key Protocol Criteria

Overall Response	Mer-vab	Pip-tazo	Difference	95% CI
Success	137/185 (74.1%)	127/181 (70.2%)	3.9%	-5.3, 13.1
Failure	41/192 (21.4%)	40/182 (22.0%)		
Indeterminate	8/192 (4.2%)	14/182 (7.7%)		
Source: FDA Statistical Reviewer				

***Reviewers' Comment**: The results for Overall Response at TOC remains qualitatively unchanged after excluding patients with major protocol violations.*

Analysis of meropenem-resistant and piperacillin/tazobactam-resistant pathogens-Study 505

To evaluate the contribution of vaborbactam, outcome of microbiologic response and Overall Response at EOIVT and TOC were examined in patients infected with meropenem-resistant baseline pathogens. There were 3 patients with meropenem-resistant pathogen in the mer-vab group and 5 patients in pip-tazo group. All three patients with meropenem resistant pathogens in the mer-vab group achieved overall success and microbiologic eradication at EOIVT and TOC visit, whereas in the pip-tazo group, 3 of 5 achieved overall success at EOIVT, and of those, 1

achieved overall success at TOC.

Table 34 Outcome Evaluation of Meropenem-Resistant baseline pathogens-Study 505

Outcome/ BL Pathogen	**Treatment Group**	
Overall Success	Mer-vab	Pip-tazo
Klebsiella pneumoniae		
EOIVT	1/1	1/1
TOC	1/1	0/1
Pseudomonas aeruginosa		
EOIVT	2/2	2/4
TOC	2/2	1/4
Eradication rate		
Klebsiella pneumoniae		
EOIVT	1/1	1/1
TOC	1/1	0/1
Pseudomonas aeruginosa		
EOIVT	2/2	2/4
TOC	2/2	1/4
Clinical Cure		
Klebsiella pneumoniae		
EOIVT	1/1	1/1
TOC	1/1	1/1
Pseudomonas aeruginosa		
EOIVT	2/2	3/4
TOC	2/2	2/4
Source: Clinical Reviewers' Analysis		

Reviewers' Comment*: Outcomes for meropenem-resistant pathogens were better in the mer-vab group as compared to pip-tazo group. Although there were two isolates of meropenem-resistant Pseudomonas aeruginosa, vaborbactam is not considered to enhance in vitro activity of meropenem against P. aeruginosa. Therefore it is difficult to ascertain added contribution of the beta-lactamase inhibitor, vaborbactam, from the results of this trial. Majority of pathogens had in vitro susceptibility to meropenem in this trial. Thus, this trial design only allows the assessment of meropenem-vaborbactam combination regimen, and it is difficult to provide any comment whether the results of assessment would be any different, if meropenem was used alone without vaborbactam in the trial.*

Table below summarizes overall success, clinical cure and microbiologic eradication at EOIVT and TOC for patients infected with piperacillin-tazobactam resistant pathogens at baseline.

Table 35 Outcome Evaluation in Patients Infected with Piperacillin/tazobactam -Resistant Baseline Pathogens (both group)-Study 505

	OREOIVT	ORTOC	OREOIVT	ORTOC
BL Pathogen	**Mer-vab N*=40**		**Pip-tazo N*= 27**	
	OREOIVT	ORTOC	OREOIVT	ORTOC
Acinetobacter species	1/1	1/1	2/2	2/2
Citrobacter freundii species	1/1	1/1	1/1	1/1
E. cloacae sp	4/4	3/4	2/2	2/2
E. faecalis	2/2	1/2	1/1	1/1
Escherichia coli	7/7	4/7	8/8	6/8
E. faecium	1/1	0/1	0/0	0/0
Klebsiella oxytoca	1/1	0/1	0/0	0/0
K. pneumoniae	15/15	9/15	8/8	3/8
P. aeruginosa	1/1	1/1	3/4	2/4
*S. saprophyticus***	5/5	4/5	0/0	0/0
Proteus mirabilis	1/1	0/1	0/0	0/0
Providencia rettgeri	1/1	0/1	1/1	1/1

Source: Clinical Reviewers' Analysis

Mer-vab: 100% Overall Response at EOIVT and 55% at TOC;
Pip-tazo: 96% Overall Response at EOIVT and 67% at TOC.
*N= Total number of piperacillin-tazobactam resistant isolates

**Note MV group had 5 patients with *S. saprophyticus infection, all were "Success" at* EOIVT
OREOIVT= Overall response at EOIVT(inked in 'black'); ORTOC= Overall Response at TOC (inked in 'blue'); BL= Baseline

***Reviewers' Comment**: Notably, in Study 505, 67 of 374 patients (18%) in the m-MITT population had an infection with piperacillin-tazobactam resistant baseline pathogens, of which 27/272 (10%) patients were in pip-tazo treatment group (as compared to 4/273 (1.5%)patients with meropenem resistant in mer-vab group).*

As evident from the table above, for patients with piperacillin/tazobactam resistant pathogens, overall response of success was comparatively higher at EOIVT in the mer-vab group as compared to pip-tazo group, whereas, overall response of success at TOC was lower in the mer-vab group as compared to pip-tazo group.

However, since the sample size is small for this subgroup, it is difficult to assess, if the overall result s of this trial was impacted by higher proportion of baseline pathogen resistance to the comparator (pip-tazo) group.

Analysis of outcome based on β-lactamase production

In Study 505, a small proportion of patients had baseline pathogen which over-expressed β-lactamase enzymes in each study group. Tables below displays the Overall Success at EOIVT and TOC by baseline pathogen based on beta-lactamase production status (positive or negative).

Table 36 Overall Success at EOIVT and TOC by Baseline Pathogen and Beta-lactamase Production Status (mMITT) - Study 505

		Endpoints			
		EOIVT		TOC	
Pathogen		Treatment Group		Treatment Group	
		Mer-vab	Pip-tazo	Mer-vab	Pip-tazo
E. coli	ESBL (+)	27/ 27 (100)	25/ 27 (93)	19/ 27 (70)	16/ 27 (59)
	ESBL (-)	92/ 94 (98)	82/ 87 (94)	77/ 94 (82)	66/ 87 (76)
E. cloacae sp	ESBL (+)	7/ 7 (100)	3/ 3 (100)	5/ 7 (71)	3/ 3 (100)
	ESBL (-)	2/ 2 (100)	1/ 1 (100)	2/ 2 (100)	0/ 1 (0)
K. pneumoniae	ESBL (+);	20/ 21 (95)	15/ 15 (100)	12/ 21 (57)	6/ 15 (40)
	ESBL (-)	8/ 8 (100)	10/ 11 (91)	5/ 8 (63)	7/ 11 (64)
Proteus mirabilis	ESBL (+)	4/ 4 (100)	2/ 2 (100)	3/ 4 (75)	2/ 2 (100)
	ESBL (-)	2/ 2 (100)	10/ 10 (100)	0/ 2 (0)	7/ 10 (70)
Pseudomonas aeruginosa	ESBL (+)	2/ 2 (100)	6/ 8 (75)	2/ 2 (100)	3/ 8 (38)
	ESBL (-)	2/ 2 (100)	2/ 2 (100)	2/ 2 (100)	1/ 2 (50)
E. faecalis	ESBL (-)	12/ 12 (100)	13/ 14 (93)	7/ 12 (58)	11/ 14 (79)
Providencia stuartii	ESBL (+);	1/1	0/0	0/1	0/0
A. baumanii	*ESBL (+) ;*	1/1	2/2	1/1	2/2

Source: Clinical Reviewers' Analysis; and Ad hoc Table 15.4
ESBL= extended spectrum beta lactamase; N= number of ESBL (+) or (-) isolates in both treatment groups

Table below presents Overall Response and Microbiologic Response at EOIVT and TOC in patients with carbapenemase producing baseline pathogen.

Table 37 Overall Response and Microbiologic Response at EOIVT and TOC in Patients with Carbapenemase Producing Baseline Pathogens; Also Displayed Corresponding Meropenem and Meropenem-Vaborbactam MIC (m-MITT population, Study 505)

								Tx Group	
Baseline Pathogen	***CARBAPEN***	***MERO MIC***	***MEVA MIC***	***MR EOIVT***	***OR EOIVT***	***OR TOC***	***MR TOC***	***Mer-Vab***	***Pip-Tazo***
Acinetobacter baumannii-sp	*OXA-23, OXA-64*	*64*	*32*	*Erad*	*Succ*	*Succ*	*Erad*		***1***
	OXA-23,	*32*	*32*	*Erad*	*Succ*	*Succ*	*Erad*		***1***

	OXA-66	*64*	*64*	*Erad*	*Succ*	*Succ*	*Erad*	***1***	
Klebsiella pneumoniae	*KPC-2*	*>64*	*1*	*Erad*	*Succ*	*Fail*	*Recur*		***1***
	OXA-48	*64*	*32*	*Erad*	*Succ*	*Succ*	*Erad*	***1***	
Proteus mirabilis	*VIM-1*	*<=0.5*	*0.5*	*Erad*	*Succ*	*Succ*	*Erad*	***1***	***1***
Providencia stuartii	*KPC-2*	*8*	*<=0.06*	*Erad*	*Succ*	*Indeter*	*Indeter*	***1***	
Pseudomonas aeruginosa	*IMP-1*	*>64*	*>64*	*Erad*	*Succ*	*Succ*	*Erad*	***1***	

Source: Clinical Reviewers' Analysis

CARBAPEN= carbapenemase; Mero= meropenem; MEVA= meropenem-vaborbactam; OR= overall response; MR= microbiologic response; Erad= eradication; Indeter=Indeterminate; Succ= Success; Tx= Treatment;

***Reviewers' Comment**: Overall in Study 505, very small numbers of pathogens were ESBL producers. Of those, Overall response at EOIVT was similar in ESBL producers versus ESBL non-producers. However, at TOC, response rate was better in patients without beta-lactamase production.*

With regards to carbapenemases, 5 baseline pathogens were positive for carbapenemase production in the mer-vab group. Of those, 3 isolates were Enterobacteriaceae (one patient was infected with Proteus mirabilis with VIM-1 (meropenem MIC <0.5µg/ml), who had overall response of success at both EOIVT and TOC. One patient was infected with Klebsiella pneumoniae expressing OXA-48 (meropenem MIC of 64 5µg/ml), with overall response of success at both EOIVT and TOC; and one patient with Providentia stuartii infection expressing KPC-2 (MIC of 8 µg/mL) with overall response of success at EOIVT, but Indeterminate at TOC). In addition there was 1 isolate of carbapenemase-producing Pseudomonas aeruginosa, and 1 isolate of carbapenemase-producing Acinetobacter baumanii sp. Overall response and microbiologic response was success in both Pseudomonas aeruginosa, and Acinetobacter baumanii infections at EOIVT and TOC.

Similar results for outcome at EOIVT and TOC were seen in patients infected with carbapenemase producing pathogen in the pip-tazo group.

This reviewer further examined the outcomes of patients in the mer-vab treatment group based on type of betalactamase mutations (or genotypes) per pathogen, and associated meropenem-MIC, which is presented in table below.

Table 38 Clinical, Microbiologic and Overall Response at TOC Based on Type of Betalactamase genes detected Per Pathogen in Meropenem-Vaborbactam Treatment Group (m-MITT, Study 505).

Table Outcome at TOC based on type of beta-lactamase mutations (genotypes) per pathogen					
PATHBL	**BETALACT**	**MERO MIC**	**MRTOC**	**ORTOC**	**CRTOC**
Acinetobacter baumannii-calcoaceticus sp	*ADC-11-like;**OXA-66**;OXA-23*	64	Eradication	Success	Cure
Citrobacter freundii species complex	*CMY-39*	<=0.5	Eradication	Success	Cure
Enterobacter cloacae species complex	*ACT-20-like;CTX-M-3;TEM-1*	<=0.5	Recurrence	Failure	Cure
	ACT-23-like;CTX-M-15	<=0.5	Eradication	Success	Cure
	ACT-25-like;CTX-M-15	<=0.5	Eradication	Failure	Cure
	OXA-1_OXA-30;ACT-25-like;CTX-M-15;TEM-1	<=0.5	Eradication	Success	Cure
	OXA-1_OXA-30;ACT-25-like;TEM-1	<=0.5	Eradication	Success	Cure
	OXA-1_OXA-30;ACT-25-like;VEB-3;CTX-M-15;TEM-1	<=0.5	Eradication	Success	Cure
	VEB-3; ACT-20-like;CTX-M-15;TEM-1	<=0.5	Eradication	Success	Cure
Escherichia coli	CMY-2	<=0.5	Eradication	Failure	Failure
	CTX-M-15	<=0.5	Eradication	Success	Cure
	CTX-M-15;TEM-1	<=0.5	Eradication	Success	Cure
			Indeter	Success	Cure
			Recurrence	Failure	Cure
	CTX-M-27	<=0.5	Eradication	Success	Cure
	CTX-M-3	<=0.5	Indeter	Success	Cure
	CTX-M-55	<=0.5	Eradication	Success	Cure
	OXA-1_OXA-30;CMY-2;CTX-M-15	<=0.5	Eradication	Success	Cure
	OXA-1_OXA-30;CMY-2;CTX-M-15;TEM-1	1	Eradication	Success	Cure
		2	Eradication	Success	Cure
	OXA-1_OXA-30;CTX-M-15	<=0.5	Eradication	Success	Cure
			Recurrence	Failure	Cure
	OXA-1_OXA-30;CTX-M-15;TEM-1	<=0.5	Recurrence	Failure	Failure
	OXA-1_OXA-30;OXA-1/30;CTX-M-15	<=0.5	Eradication	Success	Cure
	OXA-1_OXA-30;TEM-135;CTX-M-15	<=0.5	Eradication	Success	Cure
	TEM-1	<=0.5	Eradication	Success	Cure
			Recurrence	Failure	Failure
	TEM-35;CTX-M-15	<=0.5	Eradication	Success	Cure
Klebsiella pneumoniae	CTX-M-15;TEM-1;SHV-11	<=0.5	Indeter	Indeter	N/A
	CTX-M-3;SHV-11	<=0.5	Recurrence	Failure	Cure
	CTX-M-3;TEM-1;SHV-11	<=0.5	Recurrence	Failure	Cure
	DHA-1; SHV-11	<=0.5	Recurrence	Failure	Cure
	OXA-1_OXA-30; SHV-28	<=0.5	Recurrence	Failure	Cure
	OXA-1_OXA-30;CMY-4;SHV-1;CTX-M-15;TEM-1	<=0.5	Indeter	Indeter	Indeter
	OXA-1_OXA-30;CTX-M-15;SHV-11	<=0.5	Eradication	Success	Cure
	OXA-1_OXA-30;CTX-M-15;TEM-1;SHV-11	<=0.5	Eradication	Success	Cure
			Recurrence	Failure	Failure

Table Outcome at TOC based on type of beta-lactamase mutations (genotypes) per pathogen					
PATHBL	**BETALACT**	**MERO MIC**	**MRTOC**	**ORTOC**	**CRTOC**
	OXA-1_OXA-30;CTX-M-3;TEM-1;SHV-11	<=0.5	Eradication	Success	Cure
	OXA-1_OXA-30;OXA-1/30;SHV-28;CTX-M-15;TEM-1	<=0.5	Eradication	Success	Cure
	OXA-1_OXA-30;SHV-1-like;CTX-M-15;TEM-1	<=0.5	Indeter	Failure	Failure
	SHV-1;CTX-M-15;TEM-1	<=0.5	Eradication	Success	Cure
	SHV-1;OXA-9;CTX-M-15	<=0.5	Eradication	Success	Cure
	SHV-1;OXA-9;CTX-M-15;TEM-1	<=0.5	Eradication	Success	Cure
			Recurrence	Failure	Cure
		2	Eradication	Success	Cure
	SHV-1;OXA-9; **OXA-48**; CTX-M-15;TEM-1	**64**	Eradication	Success	Cure
	SHV-28;CTX-M-15	<=0.5	Eradication	Success	Cure
	VEB-3;CMY-4;SHV-1-like;CTX-M-15;TEM-1	<=0.5	Eradication	Success	Cure
Proteus mirabilis	CTX-M-3;TEM-1	<=0.5	Eradication	Success	Cure
	CTX-M-55;TEM-2	<=0.5	Eradication	Success	Cure
			Recurrence	Failure	Cure
	SHV-12; TEM-1; **VIM-1;**	<=0.5	Eradication	Success	Cure
Providencia stuartii	**KPC-2**	**8**	Indeter	Indeter	N/A
Pseudomonas aeruginosa	CARB-2_PSE-1;OXA-488;PDC-16-like	**16**	Eradication	Success	Cure
	OXA-488;IMP-1;PDC-12;OXA-10	**>64**	Eradication	Success	Cure

Source: Clinical Reviewers' Analysis;

Note: Beta-lactamase genes in red ink denotes Carbapenemases; Outcomes other than success are marked in 'red'

MIC: minimum inhibitory concentration; Mero-MIC= meropenem MIC; MRTOC=Microbiologic Response at TOC; CRTOC= Clinical Response at TOC; ORTOC=Overall Response at TOC; Indeter= Indeterminate; Recur=Recurrence; Improv=Improvement; N/A= Not Assessed;

***Reviewers' Comment**: As evident from the table above, distribution of more than one beta-lactamase gene was seen in majority of isolates. There were 19 isolates of E. coli; 20 isolates of K. pneumoniae; 1 isolate of Providentia stuartii; and 4 isolate of Proteus mirabilis with beta-lactamase producing genes in the mer-vab group. Microbiologic recurrence rates in K. pneumoniae were higher than in E. coli.*

Most of the isolates with beta-lactamase production among Enterobacteriaceae isolates in the mer-vab group had meropenem MIC within susceptible range. As shown in the table above, there does not appear to be any correlation between meropenem MIC, the presence of beta-lactamase genes in pathogens and outcomes in patients.

MIC Increases with the exposure to study treatment

The Applicant presented data on MIC increases with exposure to study treatments. Among patients who had pathogens recovered post baseline during or after treatment, a few had an MIC increase of ≥4-fold for either mer-vab or pip-tazo group.

In the mer-vab group, 3 patients (all with *K. pneumoniae* infection) had a ≥4-fold increase in meropenem-vaborbactam MIC, and 8 patients (5 patients with *E. coli*, 1 patient with *Enterococcus faecalis*, 1 patient with *P. mirabilis*, and 1 patient with *Enterobacter cloacae* complex) had a ≥4-fold increase in piperacillin/tazobactam MIC.

Of the 3 patients with *K. pneumoniae* at baseline who received mer-vab and had a 4-fold increase in MIC to meropenem-vaborbactam, 1 occurred at EOT (Patient # 100-004-501) and 2 occurred at TOC (Patient # 100-004-502 and 703-001-513). Meropenem-vaborbactam MICs increased from 0.06 µg/mL to 0.25 µg/mL in 2 patients (Patient # 100-004-501 and 100-004-502) and from 0.125 µg/mL to 0.5 µg/mL in 1 patient (patient # 702-001-513), however, all remained within the susceptible range for meropenem.
All 3/3 patients had Overall Response of Success at EOIVT. However, at TOC, 0/3 achieved Overall Response of Success(Patient# 100-004-501 was assessed as Indeterminate for Overall Response due to 'Indeterminate' microbiologic and clinical outcomes, whereas, patient #100-044-502 and # 703-001-513 achieved clinical outcome of Cure, however, their Overall Response was Failure due to microbiologic outcome of Recurrence.
The Applicant had performed a whole genome sequence analysis, showing that the baseline and the post visit isolates were likely the same organism in all 3 of these patients.

In the pip-tazo group, 7 patients (4 patients with *E. coli* and 3 with *K. pneumoniae*) had a ≥4-fold increase in MIC for piperacillin/tazobactam; and 4 patients (3 with *P. aeruginosa* and 1 with *Proteus mirabilis* infection) had a ≥4-fold increase in MIC for meropenem-vaborbactam.

Analysis of patients with Overall Response of 'Success' at EOIVT but Overall Response of 'Failure' at TOC (m-MITT)-Study 505

Since majority of baseline pathogen were meropenem sensitive in the mer-vab group, it is worthwhile to examine baseline pathogen characteristics, Charlson comorbidity index score, diabetes status, microbiologic and clinical outcome of patients who had Overall Response of 'Success' at EOIVT but Overall Response 'Failure' at TOC (m-MITT)-Study 505 (Table below).

Table 39 Selected Characteristics of Patients with Overall Response of 'Success' at EOIVT but Overall Response of 'Failure' at TOC in Meropenem-Vaborbactam Group (m-MITT)-Study 505 [Total no. of patients=38; Total no. of isolates=43]

Selected Characteristics of Patients in mer-vab group with Overall Response of 'Success' at EOIVT but Overall Response of 'Failure' at TOC in mer-vab group (m-MITT)- Study 505										
SUBJECT (N=38)	**BL PATHOGEN** (N=43)	**MERO MIC**	**ORTOC**	**MRTOC**	**CRTOC**	**CC Score**	**IFN-Type**	**DM**	**CrCl**	**Tx Dur**
076-003-504	*E. coli*	<=0.5	Failure	Recurrence	Cure	3	AP		>50	*10*
076-003-509	*E. coli*	<=0.5	Failure	Indeter	Failure	2	cUTI-RS		>50	*10*
100-002-510	*K. pneumoniae*	<=0.5	Failure	Recurrence	Cure	3	cUTI-RS		>50	*11*
100-004-502	*K. pneumoniae*	<=0.5	Failure	Recurrence	Cure	3	AP		>50	*10*
100-006-502	*K. pneumoniae*	<=0.5	Failure	Recurrence	Failure	8	cUTI-NRS	Y	>50	*11*
100-006-506	*E. coli*	<=0.5	Failure	Recurrence	Cure	2	AP		>50	*11*
100-007-508	*E. coli*	<=0.5	Failure	Recurrence	Failure	3	cUTI-NRS		>50	*10*
112-002-510	*E. cloacae sp*	<=0.5	Failure	Recurrence	Cure	0	cUTI-NRS		>50	*11*
112-004-503	*E. faecalis*	8	Failure	Eradication	Cure	2	cUTI-RS		>50	*11*
	Proteus mirabilis	<=0.5	Failure	Recurrence	Cure	2			>50	*11*
112-004-510	*K. pneumoniae*	<=0.5	Failure	Recurrence	Cure	1	cUTI-RS		>50	*11*
203-002-505	*E. coli*	<=0.5	Failure	Eradication	Failure	5	cUTI-RS	Y	>50	*11*
	K. pneumoniae	<=0.5	Failure						>50	*11*
203-002-506	*E. coli*	<=0.5	Failure	Recurrence	Failure	7	cUTI-RS	Y	>50	*11*
	Morganella morganii	<=0.5	Failure	Recurrence	Failure				>50	*11*
203-008-509	*E. coli*	<=0.5	Failure	Recurrence	Cure	1	AP		>50	*10*
300-001-506	*E. coli*	<=0.5	Failure	Recurrence	Cure	6	AP		30 - 50	*9*
300-004-504	*E. coli*	<=0.5	Failure	Recurrence	Cure	4	AP	Y	>50	*10*
604-002-503	*E. coli*	<=0.5	Failure	Recurrence	Cure	6	cUTI-RS	Y	30 - 50	*11*
604-002-505	*E. coli*	<=0.5	Failure	Recurrence	Cure	1	AP		>50	*10*
604-005-502	*E. coli*	<=0.5	Failure	Recurrence	Cure	6	AP	Y	30 - 50	*11*
642-001-510	*E. coli*	<=0.5	Failure	Recurrence	Failure	7	cUTI-NRS	Y	30 - 50	*10*
642-001-514	*E. coli*	----	Failure	Recurrence	Failure	9	cUTI-NRS		>50	*11*
642-002-503	*E. coli*	<=0.5	Failure	Recurrence	Cure	9	cUTI-NRS		>50	*11*
642-002-511	*K. pneumoniae*	<=0.5	Failure	Recurrence	Cure	4	cUTI-RS		30 - 50	*11*
703-001-502	*E. coli*	<=0.5	Failure	Recurrence	Cure	2	AP	Y	>50	*11*
703-001-513	*K. pneumoniae*	<=0.5	Failure	Recurrence	Cure	6	AP		>50	*11*
703-005-507	*K. pneumoniae*	<=0.5	Failure	Recurrence	Cure	8	cUTI-NRS	Y	>50	*11*
804-001-512	*E. coli*	<=0.5	Failure	Recurrence	Cure	8	cUTI-NRS		>50	*11*
804-001-525	*E. coli*	<=0.5	Failure	Recurrence	Cure	5	AP		>50	*10*
804-001-530	*E. faecalis*	---	Failure	Recurrence	Cure		cUTI-RS	Y	>50	*11*

Selected Characteristics of Patients in mer-vab group with Overall Response of 'Success' at EOIVT but Overall Response of 'Failure' at TOC in mer-vab group (m-MITT)- Study 505										
SUBJECT (N=38)	**BL PATHOGEN** (N=43)	**MERO MIC**	**ORTOC**	**MRTOC**	**CRTOC**	**CC Score**	**IFN-Type**	**DM**	**CrCl**	**Tx Dur**
804-002-501	*Proteus mirabilis*	<=0.5	Failure	Recurrence	Cure	3	AP		>50	*10*
804-002-534	*E. cloacae sp*	<=0.5	Failure	Eradication	Cure	3	cUTI-RS		>50	*11*
	E. faecalis	>8	Failure	Recurrence	Cure		cUTI-NRS		>50	*11*
804-002-537	*E. coli*	<=0.5	Failure	Recurrence	Cure	5	AP		>50	*11*
804-005-537	*E. coli*	<=0.5	Failure	Recurrence	Cure	11	cUTI-NRS		>50	*11*
804-005-545	*E. faecalis*	8	Failure	Recurrence	Cure	4	AP		>50	*11*
804-007-501	*K. pneumoniae*	<=0.5	Failure	Recurrence	Cure	1	cUTI-RS		>50	*11*
804-009-505	*E. faecalis*	4	Failure	Recurrence	Cure	3	cUTI-NRS		>50	*11*
804-009-523	*E. faecalis*	4	Failure	Recurrence	Cure	4	cUTI-NRS		>50	*11*
804-009-531	*E. coli*	<=0.5	Failure	Recurrence	Cure	6	cUTI-NRS		>50	*11*
840-020-502	*Unspecified Enterococcus*	---	Failure	Recurrence	Cure	1	cUTI-RS		>50	*17*
Source: Clinical Reviewers' Analysis *No. of subjects with cUTI-NRS were 12; with cUTI-RS were 12 ; and with AP were 14* cUTI-NRS= cUTI with non-removable source; cUTI-RS=cUTI with removal source; AP= acute pyelonephritis										

***Reviewers' Comment**: As displayed in the table above, in the mer-vab group, only one patient who failed at TOC did not have microbiologic recurrence. In terms of pathogen, majority of recurrences occurred in infection with E.coli (n=21), followed by K. Pneumoniae (n=9), E. faecalis (n=6), and Enterobacter cloacae species complex (n=2). One patient was co-infected with Morganella morgagni and E.coli; and one patient with unspecified enterococcus.*

In terms of comorbidities, 10 patients had underlying diabetes mellitus type-2; 16 patients had Charlson comorbidity index score of 5 or greater, and majority of patients had CrCl >50ml/min, (except 5 patients with CrCl between 30-50). None of the patients were bacteremic in this subgroup of patients.

With regards to meropenem susceptibility, all pathogens were meropenem susceptible, except E. faecalis with MICs of 4 and 8 which were reported as 'Not interpretable' per CLSI criteria.

Table below presents selected characteristics of patients in pip-tazo group with Overall Response of Success and EOIVT, however, Overall Response Failure at TOC visit in Study 505

Table 40 Selected Characteristics of Patients in Pip-Tazo Group with Overall Response of 'Success' at EOIVT but Overall Response 'Failure' at TOC (m-MITT)-Study 505

Selected Characteristics of Patients in pip-tazo group with Overall Response of "Success" at EOIVT but Overall Response of "Failure" at TOC (m-MITT)-Study 505

SUBJID (N= 32)	***INFTYP***	***DM***	***CrCl***	***BL-PATHOGEN*** *(n=38)*	***MIC***	***ORTOC***	***MRTOC***	***CR TOC***	***CCI Score***	***Tx Dur***
076-003-505	cUTI-NRS		>50	*E. coli*	*16*	*Failure*	*Recurrence*	*Cure*	*3*	*10*
076-003-507	cUTI-RS		<30	*E. coli*	*16*	*Failure*	*Eradication*	*Cure*	*9*	*11*
	cUTI-RS			*K. pneumoniae*	*4*	*Failure*	*Recurrence*	*Cure*	*9*	
100-002-503	cUTI-RS		>50	*E. coli*	*4*	*Failure*	*Recurrence*	*Cure*	*4*	*10*
				Proteus mirabilis	*<=0.5*	Failure	Eradication	Cure	4	*10*
100-002-509	AP		30 - 50	*E. coli*	*2*	Failure	Recurrence	Cure	3	*11*
100-004-504	cUTI-RS		>50	*K. pneumoniae*	*>64*	Failure	Recurrence	Cure	3	*10*
100-006-501	AP		>50	*E. coli*	*64*	Failure	Recurrence	Cure	2	*10*
100-006-510	AP	Y	>50	*K. pneumoniae*	*4*	Failure	Recurrence	Cure	8	*11*
100-007-513	cUTI-RS		30 - 50	*E. coli*	*4*	Failure	Recurrence	Cure	6	*10*
203-002-504	AP		----	*E. coli*	*2*	Failure	Recurrence	Cure	4	*10*
203-002-507	cUTI-RS		30 - 50	*E. coli*	*2*	Failure	Recurrence	Cure	8	*11*
				Proteus mirabilis	*<=0.5*	Failure	Eradication	Cure	8	*11*
203-008-502	AP		>50	*E. coli*	*>64*	Failure	Recurrence	Cure	2	*11*
300-001-508	AP		>50	*E. cloacae*	--	Failure	Eradication	Fail	5	*8*
300-001-523	cUTI-RS		>50	*K. pneumoniae*	*>64*	Failure	Recurrence	Cure	4	*10*
604-002-507	AP	Y	>50	*E. coli*	*16*	Failure	Recurrence	Cure	5	*11*
616-003-506	cUTI-NRS		>50	*E. coli*	*8*	Failure	Recurrence	Cure	5	*11*
642-001-505	cUTI-NRS	Y	>50	*K. pneumoniae*	*16*	Failure	Recurrence	Fail	4	*11*
642-002-505	AP		>50	*P. aeruginosa*	*64*	Failure	Recurrence	Cure	1	*11*
642-003-502	cUTI-RS		>50	*E. coli*	--	Failure	Recurrence	Fail	3	*9*
642-003-504	cUTI-RS		>50	*E. coli*	*2*	Failure	Recurrence	Cure	1	*8*
703-001-511	cUTI-NRS		>50	*E. coli*	*>64*	Failure	Recurrence	Cure	3	*11*
703-001-517	cUTI-NRS		----	*E. cloacae*	*4*	Failure	Recurrence	Cure		*11*
703-005-502	cUTI-NRS		>50	*K. pneumoniae*	*>64*	Failure	Recurrence	Cure	5	*11*
804-001-520	AP		>50	*E. coli*	*2*	Failure	Recurrence	Cure	4	*10*
804-002-523	AP	Y	>50	*E. coli*	*2*	Failure	Recurrence	Cure	4	*11*
804-002-529	AP		>50	*K. pneumoniae*	*>64*	Failure	Recurrence	Cure	6	*11*
804-005-541	cUTI-NRS		>50	*E. faecium*	*>64*	Failure	Eradication	Cure	0	*11*
			>50	*P. aeruginosa*	*>64*	Failure	Recurrence	Cure	0	*11*
804-005-544	cUTI-NRS		>50	*K. pneumoniae*	*>64*	Failure	Recurrence	Cure	6	*11*
804-005-546	cUTI-NRS		>50	*P. aeruginosa*	*4*	Failure	Recurrence	Cure	5	*11*
804-006-506	cUTI-RS		>50	*E. faecalis*	*4*	Failure	Eradication	Cure	4	*12*
			>50	*E. coli*	*2*	Failure	Recurrence	Cure	4	*12*
804-009-504	cUTI-RS		>50	*E. faecalis*	*8*	Failure	Recurrence	Cure	4	*11*
804-009-515	cUTI-NRS		>50	*K. pneumoniae*	*32*	Failure	Recurrence	Cure	4	*11*
840-005-507	cUTI-NRS		30 - 50	*Escherichia coli*	---	Failure	Recurrence	Cure	6	*6*

Source: Clinical Reviewers' Analysis

cUTI-NRS= 11; cUTI-RS=11; AP=11; INFTYP= Infection type; DM= Diabetes mellitus; CrCl=Creatinine Clearance; BL-PATHOGEN= Baseline pathogen; OR: Overall Response; MR= Microbiologic Response; CR= Clinical Response; CCI score= Charlson comorbidity index score; Tx DUR= Treatment Duration;

***Reviewers' Comment**: Majority of patients (except one patient) in the pip-tazo group who had Overall Response of Success at EOIVT, failed at TOC due to microbiologic recurrence similar to what is seen with the mer-vab group. Majority of recurrences occurred in infection with E.coli (n=17), followed by K. Pneumoniae (n=10), P. aeruginosa (n=3), Proteus mirabilis (n=2), E. faecalis (n=2) and E. faecium (n=1). Unlike the mer-vab group, 3 patients had infection with P. aeruginosa, which were all pip-tazo resistant at baseline. Only 4 patients had underlying diabetes mellitus, and none of the patients were bacteremic. 13 patients had CCI score of 5 or greater. Unlike in the mer-vab group, there was one patient with CrCl of <30. Majority had CrCl>50 as seen in the mer-vab group.*

With regards to pip-tazo susceptibility by CLSI criteria, 5 of 17 E. coli; 7 of 10 K. pneumoniae, 3 of 3 P aeruginosa, 1 of 1 E. faecium, were resistant to piperacillin-tazobactam; 2 of 2 E faecalis resulted as "no interpretation" with pip-tazo MIC of 4 and 8.

Secondary Endpoints

Secondary endpoints selected for this protocol were proportion of patients in the m-MITT and ME populations with Overall Response of Success at both the EOIVT and TOC visits by infection type; proportion of patients in the m-MITT and ME Populations with a microbiologic outcome of Eradication at TOC; and proportion of patients with a clinical outcome of Cure in the m-MITT, CE, and ME Populations at Day 3, EOIVT, EOT, TOC, and LFU.

Table below displays the proportion of subjects in the m-MITT with overall success at both EOIVT and TOC visits by infection type.

Table 41 Overall Success Rate at EOIVT and TOC by Infection Type (m-MITT)-505

	EOIVT			TOC	
	Mer-vab	**Pip-tazo**		**Mer-vab**	**Pip-tazo**
AP	N=120	N=101		N=120	N=101
Overall success	117/120 **(97.5)**	95/101 **(94.1)**		99/120 **(82.5)**	76/101 **(75.2)**
Difference (95% CI)	*3.4 (-2.0, 10.2)*			*7.3 (-3.5, 18.3)*	
cUTI with RS	N=35	N-38		N=35	N-38
Overall success	35/35 **(100.0)**	35/38 **(92.1)**		21/35 **(60.0)**	23/38 **(60.5)**
Difference (95% CI)	*7.9(-2.5, 20.9)*			*-0.5 (-22.7, 21.6)*	
cUTI with NRS	N-37	N-43		N-37	N-43
Overall success	37/37 **(100.0)**	41/43 **(95.3)**		23/37 **(62.2)**	29/43 **(67.4)**

Difference (95% CI)	*4.7(-5.1, 15.6)*		*-5.3 (-26.0, 15.5)*

Source CSR Study-505, Table 24

The difference estimates and the 95% CIs are obtained based on Miettinen and Nurminen method [Miettinen and Nurminen, 1985].
CI = confidence interval; cUTI = complicated urinary tract infection; EOIVT = End of Intravenous Treatment; TOC = Test of Cure. RS= Removable source of infection; NRS= Non-removable source of infection

***Reviewers' Comment**: The Overall Success rates were comparatively lower at TOC visit than at EOIVT visit in both treatment groups by infection type. The Success rate in the mer-vab group remained comparatively little higher than in the pip-tazo group at TOC in all infection types.*

Tables below summarize applicant's analysis of clinical outcome and microbiologic outcome at different study time-points (at Day 3, EOIVT, EOT, TOC, and LFU).

Table 42 Clinical Outcome at Different Study Endpoints (m-MITT population) - Study 505

Time point	Clinical Outcome	Mer-vab	Pip-tazo	Difference	95% CI
Day 3	Improvement	186/192 (96.9%)	171/182 (94.0%)	2.9%	-1.4 , 7.7
Day 3	Failure	1/192 (0.5%)	0/182 (0.0%)		
Day 3	Indeterminate	3/192 (1.6%)	6/182 (3.3%)		
Day 3	Not Assessed	2/192 (1.0%)	5/182 (2.7%)		
EOIV	Cure	156/192 (81.2%)	144/182 (79.1%)	2.1%	-6.0, 10.3
EOIV	Improvement	33/192 (17.2%)	30/182 (16.5%)		
EOIV	Failure	2/192 (1.0%)	5/182 (2.7%)		
EOIV	Indeterminate	0/192 (0.0%)	1/182 (0.5%)		
EOIV	Not Assessed	1/192 (0.5%)	2/182 (1.1%)		
EOT	Cure	179/192 (93.2%)	167/182 (91.8%)	1.5%	-4.0 ,7.2
EOT	Improvement	4/192 (2.1%)	3/182 (1.6%)		
EOT	Failure	4/192 (2.1%)	6/182 (3.3%)		
EOT	Indeterminate	1/192 (0.5%)	4/182 (2.2%)		
EOT	Not Assessed	4/192 (2.1%)	2/182 (1.1%)		
TOC	Cure	174/192 (90.6%)	157/182 (86.3%)	4.4%	-2.2, 11.1
TOC	Failure	10/192 (5.2%)	11/182 (6.0%)		
TOC	Indeterminate	3/192 (1.6%)	7/182 (3.8%)		
TOC	Not Assessed	5/192 (2.6%)	7/182 (3.8%)		
LFU	Cure	166/192 (86.5%)	143/182 (78.6%)	7.9%	0.2 ,15.7
LFU	Failure	14/192 (7.3%)	17/182 (9.3%)		
LFU	**Indeterminate**	4/192 **(2.1%)**	**12**/182 **(6.6%)**		
LFU	Not Assessed	8/192 (4.2%)	10/182 (5.5%)		

Time point	Clinical Outcome	Mer-vab	Pip-tazo	Difference	95% CI
Source: Clinical Study Report 505, Table 14.2.2.1.					

***Reviewers' Comment**: At each study time point, the difference in clinical cure rates favored mer-vab as compared to pip-tazo. From the table above it appears that mer-vab met criteria for statistically superiority for Clinical Cure at the LFU visit (Day 22-26), however, it is notable that there were significantly higher number (almost 3 times) of patients in the pip-tazo group with Indeterminate or Not Assessed outcomes at LFU visit.*

These patients with Indeterminate or Not Assessed outcomes in the pip-tazo group were further explored by this reviewer. Majority of 'Not Assessed' at LFU in the pip-tazo group were lost to follow up (with no further information provided in CRFs), except for 2 patients, who withdrew from study 'due to personal reasons'.

In the mer-vab group, 1 patient (#112-006-504) with 'Indeterminate' outcome was listed as lost to follow up at LFU; however, this patient had met key protocol violation criteria. Although this patient had protocol violation, patient was allowed to continue participation in study. This patient was classified as Clinical 'Cure' and Overall Response of 'Success' at EOIVT.

For majority of 'Indeterminate' or 'not assessed' outcomes, a reason is not provided by the applicant for either treatment group.

Table below displays microbiologic outcome at different study time points in m-MITT population.

Table 43 Microbiological Outcome at Different Study Time Points - Study 505 (m-MITT population)

Microbiological Outcome at different study endpoints					
Time point	**Clinical Outcome**	**Mer-vab**	**Pip-tazo**	**Difference**	**95% CI**
Day 3	Eradication	189/192 (98.4%)	167/182 (91.8%)	6.7%	2.6, 11.8
Day 3	Persistence	0/192 (0.0%)	6/182 (3.3%)		
Day 3	Indeterminate	3/192 (1.6%)	9/182 (4.9%)		
EOIV	Eradication	188/192 (97.9%)	168/182 (92.3%)	5.6%	1.4, 10.7
EOIV	Persistence	0/192 (0.0%)	1/182 (0.5%)		
EOIV	Recurrence	0/192 (0.0%)	2/182 (1.1%)		
EOIV	Indeterminate	4/192 (2.1%)	11/182 (6%)		

Microbiological Outcome at different study endpoints					
Time point	**Clinical Outcome**	**Mer-vab**	**Pip-tazo**	**Difference**	**95% CI**
EOT	Eradication	172/192 (89.6%)	158/182 (86.8%)	2.8%	-3.8, 9.5
EOT	Persistence	0/192 (0.0%)	1/182 (0.5%)		
EOT	Recurrence	7/192 (3.6%)	7/182 (3.8%)		
EOT	Indeterminate	13/192 (6.8%)	16/182 (8.8%)		
TOC	Eradication	132/192 (68.8%)	113/182 (62.1%)	6.7%	-3.0,16.2
TOC	Persistence	0/192 (0.0%)	1/182 (0.5%)		
TOC	Recurrence	36/192 (18.8%)	34/182 (18.7%)		
TOC	Indeterminate	24/192 (12.5%)	34/182 (18.7%)		
LFU	Eradication	132/192 (68.8%)	103/182 (56.6%)	12.2%	2.4, 21.8
LFU	Persistence	0/192 (0.0%)	1/182 (0.5%)		
LFU	Recurrence	37/192 (19.3%)	41/182 (22.5%)		
LFU	Indeterminate	23/192 (12.0%)	37/182 (20.3%)		
Source: FDA Statistical Reviewer analysis (Daniel Rubin, PhD.)					

***Reviewers' Comment**: Eradication rates at TOC were slightly higher in the mer-vab group. Recurrence rates at TOC were similar in both groups. As seen with clinical outcomes, there was comparatively greater number of patients with "indeterminate" outcomes in the control group.*

Analysis of Signs/ Symptom Response

The following tables in this subsection of the review summarize the resolution rates for the major cUTI symptoms. The subsequent table presents responses over time for the symptoms of abdominal pain, costo-vertebral angle tenderness, dysuria, fever, flank pain, nausea, suprapubic pain, urinary frequency, urinary urgency, and vomiting.

Overall, symptom resolution was similar between the mer-vab and pip-tazo groups in Study 505. Most symptoms were absent by the Day 15-19 TOC visit in both treatment groups.

Table 44 Summary of symptom absence at various time-points in Study 505 (m-MITT population)

Summary of symptom absence at various time-points in Study 505 (m-MITT population)										
Symptoms	**Baseline**		**Day 3**		**EOIV (Day 5-10)**		**TOC (Day 15-19)**		**LFU (Day 22-26)**	
	M/V	**P/T**	**M/V**	**P/T**	**M/V**	**P/T**	**M/V**	**P/T**	**M/V**	**P/T**
Abdominal pain										
Absent	70.8%	65.4%	78.1%	77.5%	92.7%	91.2%	94.8%	93.4%	94.3%	90.1%
Present	29.2%	34.1%	19.8%	19.8%	6.2%	6.0%	2.1%	1.1%	1.0%	2.7%

Summary of symptom absence at various time-points in Study 505 (m-MITT population)										
Symptoms	**Baseline**		**Day 3**		**EOIV (Day 5-10)**		**TOC (Day 15-19)**		**LFU (Day 22-26)**	
	M/V	**P/T**	**M/V**	**P/T**	**M/V**	**P/T**	**M/V**	**P/T**	**M/V**	**P/T**
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Costo-vertebral angle tenderness										
Absent	28.1%	36.3%	45.3%	47.3%	90.6%	90.7%	95.3%	94.0%	94.3%	92.3%
Present	71.9%	63.2%	52.6%	50.0%	8.3%	6.6%	1.6%	0.5%	1.0%	0.5%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Dysuria										
Absent	25.5%	31.3%	47.9%	51.6%	93.2%	90.1%	94.3%	92.3%	91.1%	90.7%
Present	74.5%	68.1%	50.0%	45.6%	5.7%	7.1%	2.6%	2.2%	4.2%	2.2%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Fever										
Absent	40.1%	36.3%	72.4%	75.3%	98.4%	96.7%	96.4%	94.0%	95.3%	92.9%
Present	59.9%	63.2%	25.5%	22.0%	0.5%	0.5%	0.5%	0.5%	0.0%	0.0%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Flank pain										
Absent	31.2%	33.0%	47.4%	42.9%	92.7%	87.9%	95.8%	94.0%	94.3%	92.3%
Present	68.8%	66.5%	50.5%	54.4%	6.2%	9.3%	1.0%	0.5%	1.0%	0.5%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Nausea										
Absent	60.4%	63.2%	90.1%	85.2%	98.4%	95.6%	96.4%	94.5%	95.3%	92.9%
Present	39.6%	36.3%	7.8%	12.1%	0.5%	1.6%	0.5%	0.0%	0.0%	0.0%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Suprapubic pain										
Absent	34.9%	41.2%	50.5%	56.6%	94.8%	90.7%	94.8%	90.7%	93.2%	90.1%
Present	65.1%	58.2%	47.4%	40.7%	4.2%	6.6%	2.1%	3.8%	2.1%	2.7%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Urinary frequency										
Absent	35.4%	37.9%	50.0%	46.2%	88.5%	89.0%	91.7%	89.0%	89.6%	86.8%
Present	64.6%	61.5%	47.9%	51.1%	10.4%	8.2%	5.2%	5.5%	5.7%	6.0%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Urinary urgency										
Absent	46.9%	43.4%	58.9%	55.5%	96.9%	94.5%	95.3%	93.4%	93.2%	91.2%
Present	53.1%	56.0%	39.1%	41.8%	2.1%	2.7%	1.6%	1.1%	2.1%	1.6%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%
Vomiting										
Absent	89.6%	92.9%	96.4%	96.2%	98.4%	97.3%	96.9%	94.0%	95.3%	92.9%
Present	10.4%	6.6%	1.6%	1.1%	0.5%	0.0%	0.0%	0.5%	0.0%	0.0%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%

Source: FDA Statistical Reviewer's Analysis
M/V = meropenem/vaborbactam (n = 192). P/T = piperacillin/tazobactam (n = 182). Symptoms are abdominal pain, costo-vertebral angle tenderness, dysuria, fever, flank pain, nausea, suprapubic pain, urinary frequency, urinary urgency, and vomiting.

The Table below displays number of these 10 symptoms reported by the patients at different time-points.

Table 45 Summary of number of symptoms present at various time points in Study 505 (m-MITT population)

Number of Symptoms	Baseline		Day 3		EOIV (Day 5-10)		TOC (Day 15-19)		LFU (Day 22-26)	
	M/V	P/T	M/V	P/T	M/V	P/T	M/V	P/T	M/V	P/T
0	0.0%	0.0%	14.6%	11.0%	74.0%	70.3%	88.0%	83.0%	87.5%	82.4%
1	1.6%	1.1%	6.2%	7.7%	13.5%	13.7%	4.2%	8.8%	3.1%	5.5%
2	4.2%	5.5%	9.9%	14.8%	6.2%	8.2%	3.6%	1.1%	3.1%	3.8%
3	8.3%	15.4%	18.2%	16.5%	2.6%	2.7%	0.5%	1.6%	0.5%	1.1%
4	22.9%	18.7%	17.7%	14.8%	2.1%	1.1%	0.0%	0.0%	0.0%	0.0%
5	17.2%	15.9%	10.9%	11.5%	0.5%	0.5%	0.0%	0.0%	0.5%	0.0%
6	17.7%	16.5%	9.4%	13.2%	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%
7	14.1%	14.3%	8.3%	6.6%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%
8	8.3%	7.7%	2.1%	0.5%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%
9	4.2%	3.3%	0.5%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
10	1.6%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Missing	0.0%	0.5%	2.1%	2.7%	1.0%	2.7%	3.1%	5.5%	4.7%	7.1%

Source: FDA Statistical Reviewers' analysis
M/V = meropenem/vaborbactam (n = 192). P/T = piperacillin/tazobactam (n = 182). Symptoms are abdominal pain, costo-vertebral angle tenderness, dysuria, fever, flank pain, nausea, suprapubic pain, urinary frequency, urinary urgency, and vomiting.

***Reviewers' Comment**: The effects of study treatment on individual symptom components and response rates were similar in both treatment groups. The symptoms generally improved over time in both treatment groups.*

Results of secondary efficacy endpoints in m-MITT, ME, and CE population are displayed in table below.

Table 46 Secondary Efficacy endpoints of Clinical Cure and Eradication rates in m-MITT, ME, and CE population (Study 505)

Secondary efficacy endpoints of Clinical Cure and Eradication rates in m-MITT, ME, and CE population (Study 505)				
Endpoint (Population) Time Point	**Mer-vab (N=192) n/N' (%)**	**Pip-tazo (N=182) n/N' (%)**	**Difference %**	**95% CI**
Overall success (m-MITT)				
EOIVT	189/192 (98.4)	171/182 (94.0)	4.5	(0.7, 9.1)
TOC	143/192 (74.5)	128/182 (70.3)	4.1	(-4.9, 13.2)
Cure rate (m-MITT)				

Day 3	186/192 (96.9)	171/182 (94.0)	2.9	(-1.4, 7.8)
EOIVT	156/192 (81.3)	144/182 (79.1)	2.8	(-0.7, 7.1)
EOT	179/192 (93.2)	167/182 (91.8)	1.9	(-2.9, 7.0)
TOC	174/192 (90.6)	157/182 (86.3)	4.4	(-2.2, 11.1)
LFU	166/192 (86.5)	143/182 (78.6)	7.9	(0.2, 15.7)
Cure rate (CE)				
Day 3	243/248 (98.0)	250/258 (96.9)	1.1	(-1.9, 4.2)
EOIVT	202/248 (81.5)	206 /258 (79.8)	1.9	(-0.2, 4.6)
EOT	235/248 (94.8)	239/258 (92.6)	2.6	(-0.8, 6.3)
TOC	231/248 (93.1)	224/258 (86.8)	6.3	(1.1, 11.7)
LFU	220/248 (88.7)	209/258 (81.0)	7.7	(1.5, 14.0)
Cure rate (ME)				
Day 3	175/178 (98.3)	164/169 (97.0)	1.3	(-2.3, 5.3)
EOIVT	148/178 (83.1)	138/169 (81.7)	0.6	(-1.5, 3.3)
EOT	170/178 (95.5)	161/169 (95.3)	0.1	(-3.8, 4.3)
TOC	164/178 (92.1)	153 /169 (90.5)	1.6	(-4.5, 7.9)
LFU	156/178 (87.6)	139/169 (82.2)	5.4	(-2.2, 13.1)
Eradication rate (m-MITT)				
Day 3	189/192 (98.4)	167/182 (91.8)	6.7	(2.6, 11.8)
EOIVT	188/192 (97.9)	168/182 (92.3)	5.6	(1.4, 10.7)
EOT	172/192 (89.6)	158/182 (86.8)	2.8	(-3.8, 9.6)
TOC	132/192 (68.8)	113/182 (62.1)	6.7	(-3.0, 16.2)
LFU	132/192 (68.8)	103/182 (56.6)	12.2	(2.3, 21.8)
Eradication rate (ME)				
Day 3	177/178 (99.4)	160/169 (94.7)	4.8	(1.5, 9.3)
EOIVT	178/178 (100.0)	166/169 (98.2)	1.8	(-0.4, 5.1)
EOT	163/178 (91.6)	156/169 (92.3)	-0.7	(-6.7, 5.3)
TOC	122/178 (68.5)	109/169 (64.5)	4.0	(-5.9, 13.9)
LFU	122/178 (68.5)	99/169 (58.6)	10.0	(-0.2, 19.9)
Source: CSR, Table 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.3.1; 14.2.3.2				

Reviewers' Comment*: Overall, Cure rates were numerically higher in the mer-vab group compared with the pip-tazo group across all populations (m-MITT, CE, and ME Populations) at Day 3, EOIVT, EOT, TOC, and LFU. In each population, the pre-specified noninferiority margin of -15% was met at all visits.*

There were no differences in Cure rates over time in patients with AP as compared with patients with cUTI (not shown in table above).

Eradication rates were similar in the mer-vab and pip-tazo groups at Day 3, EOIVT, EOT, TOC, and LFU in both the m-MITT and ME Populations. However, in both groups, the rates were higher at Day 3 and EOIVT than at EOT, TOC, and LFU.

6.1.10.2. Efficacy in Subpopulations

To explore the homogeneity of mer-vab efficacy, treatment group differences were examined for a variety of subgroups defined by baseline characteristics.
All subgroups are assessed within the m-MITT primary analysis population of randomized patients who received at least 1 dose of study drug and had a microbiologically confirmed baseline pathogen.

Overall Success Rate at TOC by Subgroups

Overall success at EOIVT, for subgroups based on age, gender, renal function, diabetes status, SIRS status, Charlson comorbidity score, and geographic region were similar in both treatment groups.

Microbiological Eradication and Clinical Cure rates at TOC visit across demographic subgroups.

The subsequent two tables below displays the results of clinical and microbiological outcomes at the TOC visit across demographic subgroups.

Table 47 Summary of Clinical Cure at the TOC visit in Demographic Subgroups of the m-MITT Population- Study 505

Subgroup	Mer-vab	Pip-tazo	Difference	95% confidence interval
Gender				
Male	58/67 (86.6%)	55/62 (88.7%)	-2.1%	-14.0% to 9.9%
Female	116/125 (92.8%)	102/120 (85.0%)	7.8%	0.0% to 16.1%
Race				
White	162/178 (91.0%)	147/169 (87.0%)	4.0%	-2.6% to 10.9%
Black	3/3 (100%)	2/2 (100%)		
Asian	4/4 (100%)	2/3 (66.7%)		
Other	5/7 (71.4%)	6/8 (75.0%)		
Age (years)				
<65	122/130 (93.8%)	96/105 (91.4%)	2.4%	-4.4% to 10.0%
65-74	30/35 (85.7%)	30/39 (76.9%)	8.8%	-9.7% to 26.6%
≥75	22/27 (81.5%)	31/38 (81.6%)	-0.1%	-20.9% to 18.6%
Region				
North America	3/3 (100%)	5/6 (83.3%)		
Europe	158/173 (91.3%)	141/163 (86.5%)	4.8%	
Asia Pacific	4/4 (100%)	2/3 (66.7%)		
Rest of World	9/12 (75.0%)	9/10 (90.0%)		
Source: FDA Statistical Reviewer's Analysis				

Table 48 Summary of Microbiological Eradication at the TOC visit in Demographic Subgroups of the m-MITT Population- Study 505

Subgroup	Treatment Group		Difference	95% confidence interval
	Mer-vab	Pip-tazo		
Gender				
Male	44/67 (65.7%)	40/62 (64.5%)	1.2%	-15.1% to 17.5%
Female	88/125 (70.4%)	73/120 (60.8%)	9.6%	-2.3% to 21.3%
Race				
White	127/178 (71.3%)	105/169 (62.1%)	9.2%	-0.7% to 19%
Black	2/3 (66.7%)	2/2 (100%)		
Asian	1/4 (25.0%)	1/3 (33.3%)		
Other	2/7 (28.6%)	5/8 (62.5%)		
Age (years)				
<65	95/130 (73.1%)	75/105 (71.4%)	1.6%	-9.7% to 13.3%
65-74	20/35 (57.1%)	19/39 (48.7%)	8.4%	-14.1% to 30.1%
≥75	17/27 (63.0%)	19/38 (50.0%)	13.0%	-11.5% to 35.5%
Region				
North America	2/3 (66.7%)	1/6 (16.7%)		
Europe	124/173 (71.7%)	105/163 (64.4%)	7.3%	-2.7% to 17.2%
Asia Pacific	1/4 (25.0%)	1/3 (33.3%)		
Rest of World	5/12 (41.7%)	6/10 (60.0%)		
Infection Type				
AP	91/120 (75.8%)	68/101 (67.3%)	8.5	-3.4, 20.5
cUTI with RS	22/ 35 (62.9%)	22/ 38 (57.9%)	5.0	-17.4, 26.7
cUTI with NRS	19/ 37 (51.4%)	23/ 43 (53.5%)	-2.1	-23.6, 19.5

Source: FDA Statistical Reviewer's Analysis, and CSR Table 14.2.3.1
AP= acute pyelonephritis; cUTI with RS= cUTI with removable source of infection; cUTI with NRS= cUTI with non-removable source of infection

***Reviewers' Comment**: In the tables above, missing outcomes are counted as failures. Reader should recall that there were a disproportionately larger number of patients with Microbiological Outcome of Indeterminate at TOC visit in the pip-tazo group (12.5% in the mer-vab and 18.7% in pip-tazo group with indeterminate microbiologic outcome). Likewise, Clinical outcome of Indeterminate or Not assessed was higher in the pip-tazo as compared to mer-vab group (4.2% in mer-vab and 7.7 in pip-tazo group).*

With respect to gender, microbiologic Eradication or clinical Cure, between the two treatment groups had similar outcomes. There were only sufficient numbers of patients identified as Caucasian and Hispanic to make comparisons within and across treatment by race possible. Patients representing Asian, Black, and American Indian racial groups were very few in number

and appropriate comparisons could not be made. Caucasian and Hispanic patients had similar outcomes with respect to microbiologic Eradication or clinical Cure between treatment groups. In the age category, majority of patients in Study 505 were <65 years old. This age group had higher rates of both microbiologic eradication and clinical cure compared to older age groups in both treatment groups. As discussed earlier, older age is a risk factor for complicated infection.

In terms of infection type, Eradication rates at TOC were higher in patients with AP in both mer-vab and pip-tazo groups (91/120 [75.8%] and 68/101 [67.3%], respectively) , compared to patients with cUTI with a removable source of infection (22/ 35 [62.9%] and 22/ 38 [57.9%]), respectively and with patients with cUTI with a non-removable source of infection (19/ 37 [51.4%] and 23/ 43 [53.5%]), respectively. This is not unexpected, as patients with AP had lesser degree of severity of illness as compared to cUTI. It is also known that cUTI with non-removable source of infection has higher chances of relapse or recurrence.

Subsequent two tables below summarize clinical Cure and microbiologic Eradication rates by other baseline subgroups at EOIVT and TOC visits.

Table 49 Summary of Clinical Cure at the EOIVT and TOC visit in various baseline subgroups of the m-MITT population (study 505)

	EOIVT				TOC			
Subgroup	**Mer-vab**	**Pip-tazo**	**Difference**	**95% CI**	**Mer-vab**	**Pip-tazo**	**Difference**	**95% CI**
CrCl								
<30	1/1 (100%)	1/1 (100%)	0.0	---	1/1 (100%)	1/1 (100%)	--	----
30-50	16/20 (80%)	15/22 (68.2%)	9.1	-8.1, 28.1	16/20 (80.0%)	19/22 (86.4%)	-6.4	-30.6 to 17.2
>50	137/169 (81.1%)	125/156 (80.1%)	2.1	-1.8, 6.6	155/169 (91.7%)	134/156 (85.9%)	5.8	-1.0 to 13.0
DM status								
Yes	27/32 (84.4%)	24/34 (70.6%)	8.8	-2.5, 23.1	27/32 (84.4%)	27/34 (79.4%)	5.0	-14.4 to 24
No	129/160 (80.6%)	120/148 (81.1%)	1.5	-2.4, 6.0	147/160 (91.9%)	130/148 (87.8%)	4.0	-2.8 to 11.2
SIRS status								
Yes	47/55 (85.5%)	44/61 (72.1%)	1.5	-6.7, 9.7	53/55 (96.4%)	49/61 (80.3%)	16.0	4.8 to 28.3
No	109/137 (79.6%)	100/121 (92.6%)	1.6	-4.7, 8.4	121/137 (88.3%)	108/121 (89.3%)	-0.9	-8.8 to 7.2
CCI Score								
≤2	67/89 (75.3%)	60/77 (77.9%)	-0.9	-6.7, 5.0	84/89 (94.4%)	71/77 (92.2%)	2.2	-5.9 to 11.1

≥3	89/103 (92.2%)	94/105 (89.5%)	5.7	0.6, 12.3	90/103 (87.4%)	86/105 (81.9%)	5.5	-4.5 to 15.5
Bacteremia								
Yes	10/12 (83.3%)	13/15 (86.7%)	-16.7	-45.4, 6.3	9/12 (75.0%)	11/15 (73.3%)	1.7	-32.9, 34.0
No	143/175 (81.7%)	128/164 (78%)	4.3	1.1, 8.8	161/175 (92.0%)	144/164 (87.8%)	4.2%	-2.3 to 11.0
Baseline pathogen								
E. coli	95/125 (76%)	92/117 (78.6%)	4.4	-0.9, 10.8	114/125 (91.2%)	101/117 (86.3%)	4.9%	-3.2, 13.3
K. pneumoniae	28/30 (93.3%)	23/28 (82.1%)	-3.3	-16.8, 9.1	25/30 (83.3%)	25/28 (89.3%)	-6.0%	-25 , 13.4
E. faecalis	12/13 (92.3%)	13/14 (92.9%)	7.1	-17.2, 32.1	13/13 (100%)	13/14 (92.9%)	7.1	-17.2, 32.1
Proteus mirabilis					5/6 (83.3%)	11/12 (91.7%)		
E. cloacae sp complex	9/10 (90%)	4/5 (80%)	0.0%	----	9/10 (90.0%)	4/5 (80.0%)	10.0%	-----

Source: Clinical Reviewers' Analysis;

CrCl= Creatinine clearance in ml/min.

Table 50 Microbiological Eradication at the EOIVT and TOC Visit in Various Baseline Subgroups of the m-MITT Population

Microbiological Eradication at the EOIVT and TOC visit in various baseline subgroups of the m-MITT population								
	EOIVT				TOC			
Subgroup	**Mer-vab**	**Pip-tazo**	**Difference**	**95% CI**	**Mer-vab**	**Pip-tazo**	**Difference**	**95% CI**
Infection type								
AP	117/120 (97.5%)	93/101 (93.1%)	4.4	-1.2, 11.4	91/120 (75.8%)	68/101 (67.3%)	8.5%	-3.4,20.4
cUTI-RS	35/35 (100%)	33/38 (86.8%)	13.2	2.5, 27.4	22/35 (62.9%)	22/38 (57.9%)	5.0%	-17.3, 26.6
cUTI-NRS	36/37 (97.3%)	41/43 95.3%)	1.9	-9.8, 13.3	19/37 (51.4%)	23/43 (53.5%)	-2.1%	-23.5, 19.4
CrCl								
<30	1/1 (100%)	1/1 (100%)	0.0	--------	1/1 (100%)	0/1 (0.0%)		
30-50	20/20 (100%)	19/22 (86.4%)	13.6	-3.9, 33.6	12/20 (60.0%)	15/22 (68.2%)	-8.2%	-35.8, 20.3
>50	165/169(97.6%)	145/156 (92.9%)	4.7	0.1, 10.1	117/169 (69.2%)	97/156 (62.2%)	7.1%	-3.3, 17.3
DM-II status								

Microbiological Eradication at the EOIVT and TOC visit in various baseline subgroups of the m-MITT population								
	EOIVT				TOC			
Yes	32/32 (100%)	31/34 (91.2%)	8.8	-2.5, 23.1	17/32 (53.1%)	20/34 (58.8%)	-5.7%	-28.7, 17.9
No	156/160 (97.5%)	137/148 (92.6%)	4.9	0.1, 10.6	115/160 (71.9%)	93/148 (62.8%)	9.0%	-1.4, 19.4
SIRS status								
Yes	54/55 (98.2%)	57/61 (93.4%)	4.7	-3.8, 14.2	45/55 (81.8%)	36/61 (59.0%)	22.8%	6.2, 38.2
No	134/137 (97.8%)	111/121 (91.7%)	6.1	0.8, 12.6	87/137 (63.5%)	77/121 (63.6%)	-0.1%	-11.8, 11.6
CCI score								
≤2	85/89 (97.8%)	74/77 (96.1%)	1.6	-4.5, 8.9	69/89 (77.5%)	59/77 (76.6%)	0.9%	-11.8, 14.0
≥3	101/103 (98.1%)	94/105 (89.5%)	8.5	2.3, 16.1	60/103 (58.3%)	50/105 (47.6%)	10.6%	-3.0, 23.8
Bacteremia								
Yes	10/12 (83.3%)	14/15 (93.3%)	-10.0	-40.2, 17.2	10/12 (83.3%)	7/15 (46.7%)	36.7	-0.7, 64.5
No	173/175 (98.9%)	152/164 (92.7%)	6.2	2.2, 11.4	115/175 (65.7%)	97/164 (59.1%)	6.6	--3.7, 16.8
Baseline Pathogen								
E. coli	123/125 (98.4%)	107/117 (91.5%)	6.9%	1.7, 13.6	91/125 (72.8%)	73/117 (62.4%)	10.4%	-1.4, 22.0
K. pneumoniae	29/30 (96.7%)	26/28 (92.9%)	3.8%	-10.7, 20.0	19/30 (63.3%)	15/28 (53.6%)	9.8%	-15.3 to 33.8
Enterococcus faecalis	13/13 (100%)	14/14 (100%)	0.0%	----	7/13 (53.8%)	12/14 (85.7%)	-31.9	-61.2, 3.4
E. cloacae sp complex	10/10 (100%)	5/5 (100%)	0.0%	----	9/10 (90.0%)	3/5 (60.0%)	30.0%	----
Proteus mirabilis	6/6 (100%)	12/12 (100%)	0.0%		3/6 (50.0%)	9/12 (75%)	25.0%	-----
P. aeruginosa	5/5 (100%)	8/10 (80%)	20%	---	5/5 (100%)	4/10 (40.0%)	60%	-----

Source: Clinical Reviewers' Analysis

CrCl: Creatinine Clearance in ml/min.; DM-II: diabetes Mellitus type-II; CCI: Charlson comorbidity index Score; RS= Removable source of infection; NRS= Non-removable source of infection

***Reviewers' Comment**: Clinical Cure and microbiologic Eradication at TOC was similar when comparing two treatment groups by other baseline subgroups. There were too few patients with creatinine clearance <30 ml/min to make any meaningful statements regarding efficacy in patients with moderate to severe renal impairment. This subgroup should be further assessed in future trials.*

All patients in both groups cleared bacteremia in study 505, however, 10/12 (83.3%) patients in the mer-vab group and 13/13(100%) in pip-tazo group achieved overall outcome of success. Of 2 patients in the mer-vab group without outcome of overall success, one patient (#804-008-506) was discontinued from study drug due to AE of tremor, and another patient (#604-004-502) was prematurely discontinued due to an AE of infusion related reaction. These patients were listed as microbiologic outcome of 'Indeterminate'.

6.1.10.3. Exploratory Endpoints

New Infection with cUTI or AP
New cUTI and AP infections were defined as isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL (other than the original baseline pathogen) from a urine culture that was accompanied by new or worsening signs and symptoms of infection since the previous visit requiring alternative antimicrobial therapy in the time period after EOT. No patients in either mer-vab or pip-tazo groups had a new AP or cUTI infection during the study as defined above.

Patients who were reported as adverse events of urinary tract infections (1.5% in each group), did not meet the above criteria for new infection.

Complicated UTI or AP Superinfection
A cUTI or AP superinfection was defined as isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL (other than the original baseline pathogen[s]) from a urine culture that was accompanied by new or worsening signs and symptoms of infection since the previous visit requiring alternative antimicrobial therapy in the time period up to and including EOT. No patients in either mer-vab or pip-tazo groups had an AP or cUTI superinfection during the course of the study.

Relapse of cUTI or AP
Relapse of AP or cUTI was defined as isolation of the same baseline bacterial pathogen(s) from culture after eradication or a positive blood culture with the same baseline pathogen that was identified as a urinary pathogen after eradication and that was accompanied by new or worsening signs and symptoms of infection since the previous visit requiring alternative antimicrobial therapy in the time period after EOT. Relapse of AP or cUTI was seen in a similar percentage of patients in the mer-vab and pip-tazo group (0.4% [1 patient] and 0.7% [2 patients], respectively)

Infection-Related ICU Readmission and Length of ICU Stay for

Infection-Related ICU Readmission
No patients in either mer-vab or pip-tazo group had an infection-related ICU readmission.

All-Cause Mortality
The rate of all-cause mortality in Study 505 was 2 patients in each treatment group. Additional details for these deaths are discussed in Section 8 of this review.

Infection-Related Hospital Readmission
No patients in either group had an infection-related hospital readmission.

6.1.10.4. Additional Analyses Conducted on the Individual Trial

All additional sensitivity analysis performed by FDA reviewers' are presented in the respective end points sections. Reader is referred to Appendix 13.10 for Ad Hoc Table for Summary of Microbiological Eradication Rate by Baseline Pathogen and MIC Breakpoints Based on FDA CFU/ml Criteria (m-MITT Population-Study 505).

6.1.11. Data Quality and Integrity – Reviewers' Assessment

In collaboration with OSI, the Site Selection Tool was utilized to choose 4 sites for inspection – Site # 300-001 (Study 505) in Greece, Site # 804-005, # 804-002, and # 804-009 in Ukraine. The results of these inspections are still pending.

The submission was relatively well-organized and based on the electronic common technical document (eCTD) format described in the ICH M2 EWG Electronic Common Technical Document Specification of 2008. The submission was straightforward to navigate with information accessible in the various modules, summaries, and clinical trial reports. Information contained in the submission was relatively complete. The applicant responded appropriately to requests for additional information. A number of issues were encountered during the review. The naming of the variables was not consistent among the datasets. For example, in some datasets the subject ID was concatenated with the Study ID and the Site ID to form the unique subject ID while in some the subject ID was the unique subject ID. Few field names were also not consistent across trials. These made it difficult to join different data set and to replicate analyses.

This clinical reviewer performed a review of the case report forms (CRFs) from Study 505 (submitted with the application package). The purpose of reviewing the CRFs included verification of the accuracy of the transcription of data from the CRFs to the database and to check for agreement (based on protocol defined criteria) with the Applicant's evaluability and outcome determinations. Any discrepancies between the clinical reviewers' blinded review of CRFs and the Applicant's assessments will be commented on in the appropriate sections of the review that follow.

While the key data transcriptions and outcome assessments were accurate, a number of discrepancies between the clinical reviewers' assessment of outcomes and the Applicant's assessments of outcomes were identified. Few issues regarding the applicant's evaluability determinations necessitated the request of additional CRFs from the Applicant for review. During CRF review, it was noted by this reviewer that, cases of death during the study period, and premature study drug discontinuations due to adverse events or patient withdrawal were not consistently assessed "failure" as pre-specified in protocol, instead were classified as "Indeterminate". Conversely, in many cases, despite meeting the clinical criteria for "cure" and microbiologic "eradication", patients were classified by Investigator as "Indeterminate". This has triggered the additional review of CRFs.

The initial CRF review also revealed the inclusion of a number of patients who did not appear to fulfill the protocol definition of cUTI or AP. In most cases, the applicant considered these protocol deviations to be minor and permitted the patients to continue in the study.

These discrepancies are summarized in the following list which includes information request by FDA reviewer and Applicant's response:

Patient Number	*Treatment*	*Comment*
505-703-005-509	*Pip-tazo*	*The patient had an SAE of death on Day 2, yet patient is classified as overall response of "Indeterminate" and not 'Failure'.* *The Applicant justified stating that EOIVT and TOC visits were not done since patient died, and therefore when a visit is not done, clinical outcome is programmed as 'Not Assessed', and microbiologic outcome as 'Indeterminate' and the overall response is 'Indeterminate'.* *-This patient should have classified as 'Failure' at both EOIVT and TOC.*

505-724-009-506	*Pip-tazo*	*The patient had an AE of lacunar infarct on day 3, and it is noted that study treatment was discontinued. However, patient is assessed as Overall Response of "Indeterminate" instead of "Failure", at EOIVT and TOC.* *Applicant justified by stating the site was queried twice and requested twice to revise the assessment to 'Failure'. The site declined to change their assessment. At the TOC Visit, the clinical outcome was 'Not Assessed' because the patient missed the visit due to being on the Stroke ward.* *-This patient should have classified as 'Failure' at both EOIVT and TOC.*
505-112-002-514	*Pip-tazo*	*Patient is classified correctly as 'Clinical Cure' at EOIVT and overall response of 'Success. However, despite meeting the clinical criteria for "Cure" at TOC, was classified as "Indeterminate". In both circumstances, microbiologic result was "Indeterminate" since urine specimen was contaminated at the EOIVT and TOC visit. As defined in the protocol, this patient should have had Overall Success at TOC.* *Applicant responded stating that patient was started on another antibiotic 2 days prior to TOC for "Pneumonia", and therefore was classified "Indeterminate".* *-This patient should have been classified as 'Success' at TOC*
505-203-002-502	*Pip-tazo*	*The patient was assessed correctly at EOIVT as 'Success' based on clinical 'improvement' and microbiologic 'eradication'. At TOC, despite clinical outcome of 'Cure', and microbiologic specimen unavailability (presumed microbiologic eradication), patient was classified as overall response of 'Indeterminate' at TOC.* *The Applicant justified by stating that IV cefotaxime and then cefuroxime (for indication other than cUTI/AP), therefore was programmed as 'Indeterminate'.* *-This patient should have been classified as 'Success' at TOC*
505-203-005-501	*Pip-tazo*	*The patient was correctly classified as 'Success' at EOIVT. At TOC, despite having clinical outcome of 'Cure' and microbiologic 'eradication' (i.e., is clearance of index infection) patient is classified 'Indeterminate'.* *Applicant justified stating that patient was given penicillin for 'tonsilopharyngitis' for one week starting the day before the TOC visit, therefore clinical outcome was marked as 'Cure' and urine culture had no growth, but these were programmed to be 'Indeterminate' because of antibiotic use tonsilopharyngitis.* *- This patient should have been classified as 'Success' at TOC*

505-203-008-507	*Pip-tazo*	*The patient had overall response of 'Success' at EOIVT by achieving clinical cure and microbiologic eradication. At TOC, despite meeting clinical criteria for 'Cure' and microbiologic criteria for 'eradication' of original pathogen (Klebsiella pneumoniae), patient was classified 'Indeterminate' in clinical, microbiological and overall response.* *The Applicant justified by stating patient received oral ofloxacin for prophylaxis of urinary tract infection at EIT visit. This antibacterial drug use resulted in the clinical outcome and microbiologic results being programmed to 'Indeterminate'.* *-This patient should have been classified as 'Success' at TOC*
505-705-002-504	*Pip-tazo*	*The patient had an overall response of 'success' at EOIVT. At TOC visit, patient had clinical improvement except for 'suprapubic pain' which was presumed to be related to start of patients' menstrual cycle. At TOC, microbiologic specimen was contaminated.* *The Applicant queried Investigator to change the assessment to 'failure' on the basis of 'suprapubic pain' which was thought to be related to menstrual periods.* *This reviewer cannot make an appropriate assessment with available information and has to rely on Investigators assessment of 'indeterminate'.*
505-804-008-506	*Mer-vab*	*The patient's Overall Response is assessed as "Indeterminate" instead of 'failure' at EOIVT. On day 3, patient developed an AE of generalized body tremor and study drug infusion was stopped, as it was thought to be related to the study drug.* *The Applicant justified by stating, that the EOIVT Visit was not done, the clinical outcome and microbiologic outcome were programmed 'Not Assessed and 'Indeterminate' respectively.* *-This patient should have been classified as 'Failure' at both 'EOIVT' and TOC.*
505-076-003-510	*Mer-vab*	*The patient is classified as Overall Response of 'Indeterminate' and not 'Failure'. Patient died of broncho aspiration five days after EOIVT visit. The patient had no assessment performed at TOC visit.* *The Applicant justified that the clinical outcome and microbiologic outcome at TOC were programmed 'Not Assessed and 'Indeterminate' respectively because of this missed visit.* *-This patient should have been classified as 'Failure' at TOC*

505-203-002-503	*Mer-vab*	*The patient is classified as 'Indeterminate' at TOC despite having an SAE of 'Sudden cardiac death' after EOIVT visit but prior to EOT.* *The Applicant justified stating that the patient died of sudden cardiac death prior to EOT. Therefore, there was no TOC visit and clinical outcome and micro outcome were programmed as 'Not Assessed' and 'Indeterminate' respectively.* *-This patient should have been classified as 'Failure' at TOC*
505-300-001-501	*Mer-vab*	*The patient is correctly classified as 'Success at EOIVT by clinical outcome of 'cure' and microbiologic 'eradication'. However, at TOC, despite meeting criteria for 'Failure', overall assessment is 'Indeterminate'. There is no examination performed per CRF at TOC visit. Microbiologic results consistent with 'persistence' of baseline organism (E. coli at 5 logs).* *The Applicant justified stating that the patient missed the TOC Visit and therefore, the clinical outcome and microbiologic outcomes were 'Not Assessed' and 'Indeterminate' respectively. At the Late Follow-up (LFU) Visit, since E. coli returned (10^5 CFU/mL) this was programmed as 'Recurrence'.* *-This patient should have been classified as 'Failure' at TOC.*
505-616-006-501	*Mer-vab*	*The patient is incorrectly classified at EOIVT (performed on Day-4) as 'success' with clinical outcome of 'Cure' despite having continued nausea, vomiting, and abdominal pain. On same day (Day-4), patient withdrew consent due to development of AE (moderate) of diarrhea and severe weakness, and patient left the hospital. Furthermore, Overall Response at TOC is assessed as "Indeterminate," and not "Failure."* *The Applicant justified that the Investigator did not feel these adverse events were related to study drug and confirmed that the patient withdrew consent prior to these AEs. Therefore, the clinical outcome was marked 'Cure' at EOIVT. Because the patient withdrew consent, there was no TOC Visit performed and therefore, clinical outcome and microbiologic outcome were programmed as 'Not Assessed' and 'Indeterminate' respectively. This reviewer strongly believes that this patient should have been classified as 'failure'. There were several changes made in case report form at later dates.* *- This patient should have been classified as 'Failure' at both*

		EOIVT, and TOC.
505-705-001-502	*Mer-vab*	*The patient is 'Success' at EOIVT based on clinical outcome of "Cure". However, at TOC, despite patient having onset of some new clinical symptoms of urgency, dysuria, was classified as clinical outcome of 'Indeterminate'.* *The Applicant justified stating, Site was queried twice to change the assessment to failure as there were new onset of urinary frequency and dysuria. The Investigator did not agree to change the assessment.*

While a number of discrepancies were detected between the Applicant's and clinical reviewers' assessments, none of these discrepancies altered the primary efficacy analysis population and assessment at EOIVT visit. Although re-adjudication of these outcomes would have lowered 'success' rates at TOC in mer-vab group, efficacy would have been similar between two treatment groups at TOC.

6.1.12. Onset, Duration, and Durability of Efficacy Effects

No studies were conducted to examine the long-term effectiveness of meropenem-vaborbactam. However, PK-PD guided dosage regimen was designed by the applicant to minimize the selection of resistance (Reader is referred to section 4.5 for additional details).

Reviewers' Comment*: Given the treatment course of 5-10 days (maximum of 14 days), and its short half-life, meropenem-vaborbactam is not expected to have any persistence of effect for more than 24 hours after the end of therapy.*

6.1.13. Reviewers' Conclusion

Based on the data provided for this pivotal Phase 3 trial, the following conclusions can be made:

Patients were well balanced across both treatment groups with regard to demographics and other baseline characteristics.

The number of patients described as belonging to Asian, Black, or American Indian or African American racial groups and the number of patients with CrCl<30 were too few to make any conclusions regarding therapeutic effect (or safety) in these populations feasible.

Based on the protocol defined primary efficacy endpoint, meropenem-vaborbactam demonstrated non-inferiority and met statistical criteria for superiority at EOIVT visit. However, superiority was not demonstrated at the TOC visit, and these results have not been confirmed in a second study, therefore, the conclusions of superiority of meropenem-vaborbactam over piperacillin-tazobactam could not be reliably made. However, meropenem-vaborbactam provided evidence of non-inferiority. The noninferiority results were relatively insensitive to the handling of missing or indeterminate data and study sites with significant protocol violations.

The Clinical Cure rates and Microbiological eradication rates were supportive of non-inferiority of meropenem-vaborbactam across different time-points and rates of symptom resolution appeared similar between the two treatment groups.

In Study 505, the rates of overall success at EOIVT, Cure, and Eradication were similar in the meropenem-vaborbactam and piperacillin-tazobactam groups for subgroups defined by age, gender, geographic region, comorbidities, presence of diabetes mellitus, renal insufficiency, or presence of concurrent bacteremia.

6.2. **Study 506**

The Applicant submitted interim data from an ongoing Phase 3 trial, Study 506. Th results of this study is non-interpretable at this time due to the study's ongoing nature, a small number of patients included in the interim analysis and other statistical limitations. In addition, an open label design, different enrollment criteria and endpoints do not allow pooling efficacy results of study 506 with study 505. This trial is reviewed and presented in brief below. Only safety data were pooled from this trial for safety analysis.

6.2.1. Study Design

Overview and Objective

The purpose of this study was to evaluate the fixed combination of meropenem 2 g vaborbactam 2 g compared to Best Available Therapy (BAT) for the treatment of patients with severe gram-negative infections, including cUTI including AP, hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP), complicated intra-abdominal infections (cAI), or bacteremia (BSI), suspected or known to be caused by carbapenem-resistant Enterobacteriaceae (CRE).

The objective of this study was to evaluate the safety, tolerability, PK, and efficacy of meropenem 2 g-vaborbactam 2 g in the treatment of patients with selected serious infections, suspected or known to be due to CRE.

Trial Design

Study 506 is an ongoing, Phase 3, open label, multicenter, randomized, study of meropenem 2 gvaborbactam2 g versus BAT in the treatment of subjects with selected serious infections, specifically cUTI/AP, cIAI, HABP/VABP, and bacteremia, suspected or known to be caused by CRE.

Subjects with either a known or suspected CRE infection who were expected to need at least 7 days of treatment with IV antibacterial drugs are being enrolled in a 2:1 ratio to one of the following groups:
-Meropenem 2 g-vaborbactam 2 g IV q8h, with each dose infused for 3 hours for up to 14 days; or
-BAT with the following IV antibacterial drugs either alone or in combination for up to 14 days: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycosides (amikacin, tobramycin, or gentamicin), polymyxin B, or ceftazidime-avibactam alone.

The dosing of meropenem/vaborbactam could be adjusted according to renal function, as described in the table below. These adjustments were based in part on a separate Phase 1 renal insufficiency study.

Table 51 Study 506 Dose Adjustment Based on Renal Function

Estimated creatinine clearance mL/min (Cockcroft-Gault)	Meropenem/vaborbactam dosage regimen (all doses infused over 3 hours)
≥50	Meropenem(2g)/vaborbactam(2g) q8h
≥30-49	Meropenem(1g)/vaborbactam(1g) q8h
≥20-29	Meropenem(1g)/vaborbactam(1g) q12h
≥10-19	Meropenem(500mg)/vaborbactam(500mg) q12h
<10	Meropenem(500mg)/vaborbactam(500mg) q24h
Source: Clinical Study Protocol, Study-506, Table 6. Subjects with an estimated clearance <10 mL/min are required to receive dialysis at least twice per week. q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours.	

Study time points were as follows.

- Screening visit.
- A treatment period from 7-14 days.
- An end of treatment (EOT) visit on the final day of treatment.
- A test of cure (TOC) visit 7±2 days following the EOT visit.

- A late follow-up (LFU) visit 14 ±2 days following the EOT visit.

Randomization was stratified by presenting indication (cUTI or AP, cIAI, HABP, VABP, and bacteremia) and by region (North America, Europe, Asia Pacific, and Rest of World). The study consisted of the following periods:

1. A screening and randomization period of 1 day
2. A treatment period of 7 days to 14 days with Day 1 the first day of study drug administration and End of Treatment (EOT) the final day of study drug administration (+1 day)
3. A follow-up period of 5 days to 16 days, including a Test of Cure (TOC) visit (±2) days following EOT and Late Follow-Up visit (LFU) 14 (±2) days following EOT

Total duration of study participation was approximately 29 days with a maximum duration of 31 days.

The design and assessment schedule are described in the subsequent diagram and table.

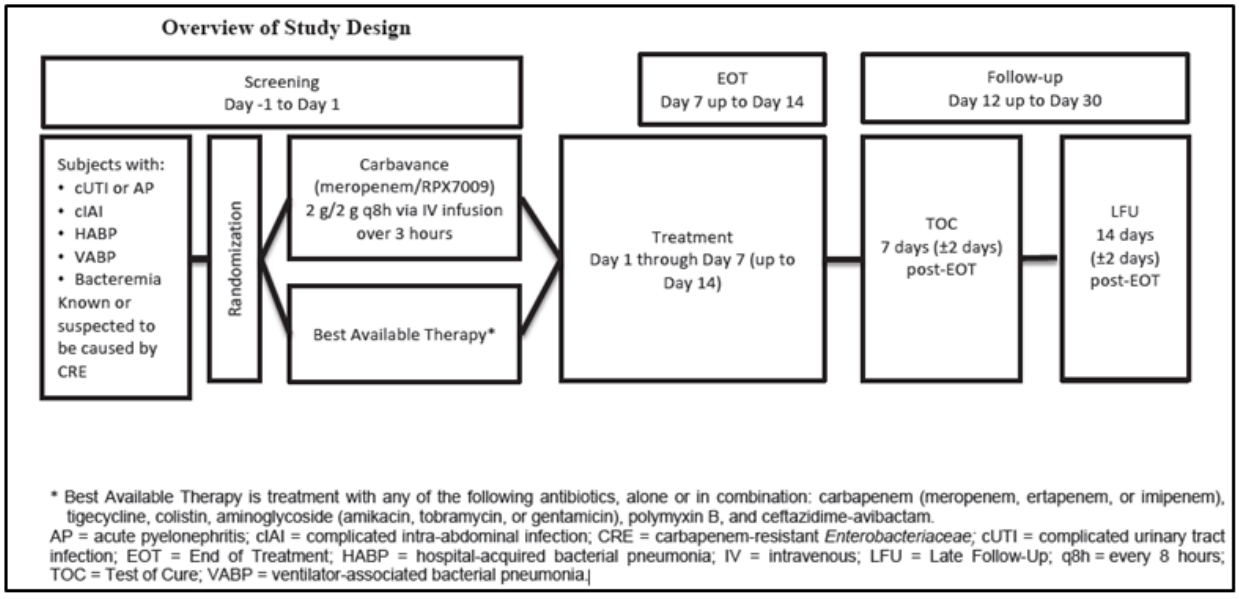


Figure 5 Overview of Study 506 Design [Source: Interim Clinical Study Report 506, Figure 1.]

Table below presents schedule of assessments for Study 506.

Table 52 Study 506 Schedule of Assessments

	Screening	Treatment									Follow-Up		
Day	-1 or 1[a]	1[a]		2	3	4	5	6	7	8-14	EOT[b] (+1 day)	TOC[c] EOT + 7 (±2) days	LFU[d] EOT + 14 (±2) days	Early Termination[e]
Assessment/Procedure		Pre Dose	Post Dose											
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Medical history	X													
Prior/concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X
Demographics[f]	X													
Height and weight[g]	X													
Complete physical examination[g]	X				X		X		X		X			X
Limited physical examination[g]				X		X		X		X		X	X	
Chest x-ray, MRI, or CT scan[p]	X											X		
Assessment of signs & symptoms (Unblinded)[h]	X	X		X	X	X	X	X	X	X	X	X	X	X
Assessment of signs & symptoms (Blinded)[q]		X									X	X		
Assessment of clinical outcome (Unblinded)					X				X		X	X	X	X
Assessment of clinical outcome (Blinded)[q]											X	X		
Vital signs[i]	X	X			X				X		X	X	X	X
Randomization to treatment arm		X												
Pregnancy test[j]	X	X									X[j]			X[j]
Screening laboratories[k] (Local laboratory)	X													
Hematology[l] (Central laboratory)		X			X				X		X	X	X	X
Serum chemistry[l] (Central laboratory)		X			X				X		X	X	X	X
Urinalysis[l] (Central laboratory)		X			X				X		X	X	X	X
Pharmacokinetic sampling[m]			X		X		X							
12-lead electrocardiogram	X										X			X
Blood culture[n]	X			X	X	X	X	X	X	X	X			
Infection-site specific sample for culture[o]	X				X				X		X	X	X	X
Study drug administration			X	X	X	X	X	X	X	X	X			
Assessment of adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

a. Screening/baseline procedures may be performed up to 24 hours prior to the first dose of study drug. All screening procedures must be completed PRIOR to randomization and the first dose of study drug (Day 1). The date of the first dose of study drug will be considered Day 1, and subsequent study days are defined by calendar days thereafter.
b. All subjects will be assessed on their last day of treatment (any time from Day 7 to Day 14). The EOT visit activities should occur within 24 hours of last dose of study drug. If EOT is on Day 7, visit activities will be combined. If a subject's treatment is changed after 72-hours post-randomization, EOT procedures will be performed and the subject will complete further visits as planned.
c. The TOC visit will occur 7 days (±2 days) after EOT, between Day 12 and Day 23. Any subject receiving treatment for less than 7 days should have a TOC visit on Day 12 (+2 days).
d. The LFU visit will occur 14 days (±2 days) after EOT, between Day 19 to Day 30. The LFU visit should be performed in-house (with limited physical examination) if at all possible. If not possible, a phone call to assess the subject's wellbeing may be substituted. Any subject receiving treatment for less than 7 days should receive an LFU visit on Day 19 (+2 days). For outpatient subjects with an LFU visit occurring before Day 28, a phone call to assess survival will be made on Day 28.
e. Subjects are expected to complete all study visits. In circumstances where a subject discontinues the study early, early termination visit procedures are required.
f. Demographic data will be collected, including name, sex, age, race, weight, and alcohol use.
g. Height will be taken at screening only. A limited, symptom-based, physical examination will be performed at indicated visits. If a subject does not display symptoms, no limited physical examination needs to be performed.
h. Assessment of signs and symptoms will include assessments to classify as new onset, continuing (increased, decreased, no change), or resolved (returned to pre-infection state) indication-based symptoms as outlined in the protocol.
i. Vital signs include blood pressure, heart rate, respiratory rate, and temperature. Vital signs should be captured at approximately the same time as the Signs and Symptoms assessment.
j. A urine and serum pregnancy test will be performed before the first dose of study drug in women of childbearing potential, however, only urine results are required to initiate treatment. A urine and serum pregnancy test will be performed as part of EOT/early termination procedures.
k. Screening laboratories will be processed/analyzed by the local laboratory within 48 hours of randomization and include: AST, ALT, total bilirubin, creatinine, WBC count with differentials, platelet count, and LCE in urine.
l. Laboratory samples will be collected, processed, and sent to the central laboratory for analysis. Hematology includes complete blood count (with red blood cell count, total WBC count with differential counts, platelet count, hemoglobin, and hematocrit). Serum chemistry includes creatinine, estimated creatinine clearance, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, uric acid, lipase, amylase, albumin, total protein, glucose, sodium, potassium, chloride, carbon dioxide, calcium, and phosphorus. Urinalysis includes dipstick analysis of protein, glucose, ketones, bilirubin, blood, nitrites, LCE, and urobilinogen; microscopic evaluation for red blood cells, WBCs, bacteria, and casts; specific gravity; and pH.
m. For subjects randomized to Carbavance (meropenem/RPX7009) only: Day 1 plasma PK samples will be collected within 30 minutes and 2 to 3 hours after the end of the first infusion. Day 3 and Day 5 plasma PK samples will be collected within 30 minutes after the end of one of that day's infusions.
n. Blood cultures are required from all study participants at baseline. All subjects with bacteremia will have daily blood cultures collected until the first negative blood culture (culture reading at 24 hours or more). Subsequent blood cultures may be collected at the Investigator's discretion, but are not required. Isolates from each positive culture will be sent to the central laboratory.
o. An adequate and appropriate infection site-specific specimen based upon diagnosis (e.g., cUTI or AP, cIAI, HABP, or VABP) should be obtained immediately prior to the first dose of study drug (or for cIAI, 96 hours before or 24 hours after the first dose of study drug) and submitted to the local microbiology laboratory for culture and susceptibility testing. If the screening sample for culture is taken per standard of care before the subject or the subject's legal representative signs informed consent, that isolate may be used for baseline and sent to the central laboratory once consent is obtained as long as the sample was collected within 72 hours (96 hours for cIAI) of the first dose of study drug. Additional samples for culture should also be collected at the specified time points. If at any point in the study a subject fails while on therapy, an adequate and appropriate specimen should be obtained prior to the initiation of a new treatment. When bacteremia is a subject's primary index infection, daily blood cultures will be collected until the first negative blood culture (culture reading at 24 hours or more). When cIAI is the subject's baseline infection, post-baseline samples should be collected as clinically indicated.
p. A chest x-ray, MRI, or CT scan done within 48 hours of enrollment is acceptable.
q. The Blinded Investigator will be responsible for establishing a baseline level of health and performing outcome assessments independent of the unblinded staff per the Blinded Adjudication Charter.

ALT = alanine aminotransferase; AP = acute pyelonephritis; AST = aspartate aminotransferase; CT = computed tomography; cUTI = complicated urinary tract infection; cIAI = complicated intra-abdominal infection; EOT = End of Treatment; HABP = hospital-acquired bacterial pneumonia; LCE = leukocyte esterase; LFU = Late Follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; TOC = Test of Cure; VABP = ventilator-associated bacterial pneumonia; WBC = white blood cell.

Source: Module 5.3.5.1, CSR Study 506 protocol

Study Population

Patients enrolled in the study had infection types of cUTI/AP, HABP/VABP, cIAI, or bacteremia as defined in the table below.

Table 53 Study 506 Infection Type Definitions

Infection Type	Definition
cUTI	A urinary infection occurring in a subject with a structural or functional abnormality of the genitourinary tract associated with clinical signs and symptoms
AP	An acute infection of the renal pelvis or parenchyma associated with clinical signs and symptoms
cIAI	An infection in the abdominal cavity which extends beyond the hollow viscus of origin (bowel, stomach, gallbladder, etc.) into the peritoneal space and that was associated with either abscess formation or peritonitis with clinical signs and symptoms
HABP	An acute infection of the pulmonary parenchyma that was associated with clinical signs and symptoms and a new pulmonary infiltrate in a subject hospitalized for more than 48 hours or in a subject admitted from a long-term acute care or rehabilitation center or admitted from home ≤7 days after discharge from a hospital or health care facility
VABP	An acute infection of the pulmonary parenchyma that was associated with clinical signs and symptoms and a new pulmonary infiltrate beginning more than 48 hours after a subject received ventilator support via an endotracheal (or nasotracheal) tube
Bacteremia	Defined by the presence of a bacterial pathogen in a blood culture that was not a contaminant. Subjects enrolled with the indication of bacteremia did not have concurrent HABP, VABP, cIAI, or cUTI/AP infections. However, subjects enrolled with HABP, VABP, or cUTI/AP might also have had concurrent secondary bacteremia
Source: CSR ,REMPEX- 506, Table 1 AP = acute pyelonephritis; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia.	

All patients were also required to have either a known or suspected CRE based on the criteria described in Table below.

Table 54 Criteria for known or Suspected CRE; Study 506

CRE Status	Criteria
Known CRE	• Had a known CRE infection based on evidence from CRE culture or other phenotypic or molecular testing within 72 hours prior to Day 1, alone or as a single isolate of a polymicrobial infection; • Had received no more than 24 hours of an antimicrobial agent to which the known CRE was susceptible prior to enrollment; OR • Had documented clinical evidence of failure after at least 48 hours of treatment with an antimicrobial agent to which the known CRE was susceptible
Suspected CRE	• Had a suspected CRE infection based on evidence from CRE culture (KPC-producing, if known) or other phenotypic or molecular testing, alone or as a single isolate of a polymicrobial infection, from any source within 90 days prior to Day 1;

	• Had received no more than 24 hours of empiric antimicrobial therapy for gram-negative organisms prior to enrollment
Source: CSR REMPEX- 506, Table 2 CRE = carbapenem-resistant *Enterobacteriaceae*; KPC = Klebsiella pneumoniae carbapenemase.	

The inclusion criteria for the trial are listed below. Subjects were to have met all criteria in order to be eligible.

1. Willingness to comply with all study activities and procedures and to provide signed written informed consent prior to any study procedures. If a subject was unable to provide informed consent due to their medical condition, the subject's legal representative was to be provided with study information in order for consent to be obtained.
2. Hospitalized male or female, ≥18 years of age.
3. Weight ≤185 kg.
4. Have a confirmed diagnosis of a serious infection, specifically cUTI or AP, cIAI, HABP, VABP, or bacteremia requiring administration of intravenous antibacterial therapy.
5. Known or suspected CRE infection. For known CRE infection, there was to be evidence from CRE culture or other phenotypic or molecular testing within 72 hours of Day 1, alone or as a single isolate of a polymicrobial infection. In addition, for known CRE infection the subject was to have received no more than 24 hours of an antimicrobial agent to which the known CRE was susceptible, except in cases of documented clinical evidence of failure after at least 48 hours of treatment. For suspected CRE infection, there was to be evidence from a CRE culture or other phenotypic or molecular testing, alone or as a single isolate of a polymicrobial infection, from any source within 90 days prior to Day 1 of the study. In addition, for suspected CRE the subject was to have received no more than 24 hours of empiric antimicrobial therapy for Gram-negative organisms prior to enrollment.
6. Expectation, in the opinion of the investigator, that the subject's infection will require treatment with intravenous antibiotics for a minimum of 7 days.
7. Expectation that subjects with an estimated creatinine clearance <10 mL/min (Cockcroft-Gault) will receive hemodialysis at least 2 times per week.
8. Diagnosis with cUTI or AP, cIAI, HABP, VABP, or BSI as defined in the tables below. For cUTI and AP there was to be the expectation, in the judgment of the investigator, that any indwelling urinary catheter or instrumentation would be removed or replaced before or as soon as possible, but not longer than 12 hours after randomization. For cIAI, patients were to be enrolled approximately 24 hours before or 96 hours after the surgical procedure when there was the expectation that operative drainage/debridement/removal of any intra-abdominal collection or other potential source of cIAI was to be performed, and an expectation that cultures from this procedure would be sent for microbiological evaluation including Gram stain, culture, and susceptibility testing.

9. Female subjects of childbearing potential, including those who are less than 2 years post-menopausal, must agree to, and comply with, using 2 highly effective methods of birth control (i.e., condom plus spermicide, combined oral contraceptive, implant, injectable, indwelling intrauterine device, sexual abstinence, or a vasectomized partner) while participating in this study. In addition, all women of childbearing potential must agree to continue to use 2 forms of birth control throughout the study and for at least 30 days after administration of the last dose of study drug.

Reviewers' Comment*: This study allowed for the inclusion of patients with moderate to severe renal dysfunction, neutropenia, neuromuscular disorders, elevated liver function tests, a history of seizures, and subjects on immunosuppressive medications.*

The following exclusion criteria were specified in the protocol:

1. History of any significant hypersensitivity or severe allergic reaction to any beta-lactam antibiotics (e.g., cephalosporins, penicillins, carbapenems, or monobactams).
2. Known or suspected likely infection with New Delhi metallo- (NDM), Verona integrin-encoding metallo- (VIM), or imipenemase-metallo-beta-lactamases or oxacillinase (OXA)-beta-lactamases (i.e., Class B or Class D beta-lactamases).
3. For subjects to be enrolled with the primary indication of cUTI or AP, any of the following urologic conditions:
    a. Likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (e.g., subjects with vesico-ureteral reflux);
    b. Suspected or confirmed prostatitis;
    c. Requirement for bladder irrigation with antibiotics or for antibiotics to be administered directly via urinary catheter;
    d. Previous or planned crystectomy or ileal loop surgery;
    e. Uncomplicated UTI (for example, female subjects with urinary frequency, urgency or pain or discomfort without systemic symptoms or signs of infection);
    f. Complete, permanent obstruction of the urinary tract;
    g. Suspected or confirmed perinephric or renal corticomedullary abscess;
    h. Polycystic kidney disease; or
    i. Any recent history of trauma to the pelvis or urinary tract.
4. For subjects to be enrolled with the primary indication of cIAI, any of the following conditions:
    a. Incomplete drainage of suspected or known intra-abdominal source;
    b. Likely to receive ongoing antibacterial drug prophylaxis or chronic suppressive therapy after intravenous treatment of cIAI;

   c. Source of infection thought to be related to or involving a non-removable prosthesis (e.g. intra-abdominal mesh) or implantable device, line (e.g., peritoneal catheter) or stent (e.g., biliary stent);
   d. Uncomplicated intra-abdominal infection, such as simple appendicitis, simple cholecystitis or gangrenous cholecystitis without rupture;
   e. Patients with infected necrotizing pancreatitis or pancreatic abscess;
   f. Patients whose surgery will include staged abdominal repair or "open abdomen" technique, or marsupialization;
   g. Patients in whom the intra-abdominal process is deemed not likely to be infectious in origin; or
   h. Non-intra-abdominal infection (e.g., infection or abscess of the abdominal wall without extension into the intra-abdominal cavity).
5. For subjects to be enrolled with the primary indication of HABP or VABP, any of the following conditions:
   a. Diagnosis of ventilator-associated tracheobronchitis; or
   b. Inability to obtain proper respiratory specimens for culture.
6. For subjects to be enrolled with the indication of bacteremia unrelated to cUTI or AP, cIAI, HABP, and VABP, any of the following:
   a. Unverified CRE infection; or
   b. Source of infection thought to be related to or involving a non-removable or implantable device or line.
7. Evidence of immediately life-threatening disease where in the opinion of the investigator, the subject is unlikely to survive more than 72 hours from randomization.
8. If calculated, an Acute Physiology and Chronic Health Evaluation (APACHE) II score >30.
9. Known or suspected endocarditis, meningitis, or osteomyelitis.
10. Irremovable or implantable device or line thought to be the potential source of infection.
11. Evidence of significant hepatic hematological or immunologic disease or dysfunction determined by any of the following:
   a. Known fulminant viral hepatitis;
   b. Subjects meeting Hy's criteria of ALT or AST >3xULN and total bilirubin >2xULN and no other explanation such as hepatitis or acute liver injury, etc.;
   c. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy; or
   d. Human immunodeficiency virus with either a CDR count <200 cells/mm^3 at the last measurement, or current diagnosis of another Acquired Immune Deficiency Syndrome-defining illness.
12. Women who are pregnant or breastfeeding.
13. Require the use of inhaled antibiotics.

14. Participation in any other study involving administration of an investigational agent or device within 30 days prior to randomization into this study or previous participation in the current study.
15. Previous participation in a study of vaborbactam.
16. Any condition that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the data.

Concomitant Antibacterial Therapy

With respect to concomitant Gram-negative antibacterial therapy, subjects in the mer-vab group with cUTI or AP were to receive the study drug as monotherapy. Those with cIAI, HABP/VABP, or BSI could receive supportive aminoglycoside therapy until culture information was available or for the first 72 hours.

The primary efficacy endpoint was defined according to the baseline infection type:

- For subjects with HABP, VABP, or BSI at baseline, the primary efficacy endpoint was Day 28 all-cause mortality.
- For subjects with cUTI or AP at baseline, the primary efficacy endpoint was overall success at the TOC visit. Overall success required both microbiological eradication (baseline pathogens reduced to $<10^4$ CFU/mL or urine) and a Clinical Outcome of cure, as defined below. A separate microbiological eradication primary endpoint was also defined for the EMA for cUTI or AP patients, which will not be a focus of this review.
- For patients with cIAI at baseline, the primary efficacy endpoint was a Clinical Outcome of cure at the TOC visit, which will be defined below.

For patients with each type of indication, Clinical Outcome endpoints were defined at different time points according to the table below. These endpoints were based on the investigator's determination of response.

As noted above for patients with cUTI or AP, microbiological eradication was defined for FDA as demonstration that the baseline pathogen(s) were reduced to $<10^4$ CFU/mL on urine culture and a negative blood culture (after a positive blood culture at baseline). For subjects with BSI, microbiological eradication was defined as demonstration that the baseline pathogen(s) were absent with repeat culture.

This was an open-label study; therefore, the investigators, study coordinators, and pharmacy staff were unblinded. However, patients were not to be explicitly informed of their treatment group assignment. In addition, each study site was to designate a blinded investigator who was to be blinded to treatment assignments and evaluate clinical outcome criteria during study visits. There was also a blinded adjudication committee to evaluate clinical outcomes in cases where the investigator's and blinded investigator's assessments were discordant. The

adjudication committee decision was to be used if the principal investigator's assessment did not agree with the blinded investigator's assessment for Clinical Outcome at the TOC visit.

Table 55 : Study 506 criteria for Clinical Outcome

Category	Criteria
Cure	Complete resolution or significant improvement of the baseline signs and symptoms, such that no further surgical intervention (cIAI only) or antimicrobial therapy is warranted. **This outcome category will only be used at Day 7, EOT, TOC, and LFU visits.**
Improvement	Lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms, but continued therapy is warranted. **This outcome category will only be used at Day 3 and Day 7 visits.**
Failure	Subjects who experience any **one** of the following: • At any study visit, worsening of baseline clinical signs and symptoms or the development of new clinical signs and symptoms of infection, sufficient to stop study medication and initiate non-study antimicrobial or for cIAI require unplanned surgical procedures or percutaneous drainage; • Surgical site wound infection (cIAI only); • At TOC and LFU visits, persistence, incomplete resolution of baseline clinical signs and symptoms of infection; • Withdrawal from the study due to an adverse event or due to lack of clinical improvement; or • Death of the subject during the study.
Indeterminate	Clinical outcome cannot be determined.

EOT = End of Treatment; LFU = Late Follow-up; TOC = Test of Cure.

Source: REMPEX-506, Table 3; Statistical Analysis Plan

Statistical Methodologies - Study 506

This study was not designed for inferential statistical hypothesis testing. Thus, it was considered a descriptively analyzed study. However, as was noted in the previous subsection, the trial did define an indication-specific primary efficacy endpoint. In addition, a primary efficacy analysis population was defined as the mCRE-MITT population of randomized subjects who received at least 1 dose of study drug and had confirmed baseline CRE infection. This population and other analysis populations defined in the statistical analysis plan are described below.

- The intent-to-treat (ITT) population was comprised of all randomized subjects.
- The modified intent-to-treat (MITT) population was comprised of all subjects who met the ITT criteria and received at least 1 dose of study drug as randomized.
- The safety population was comprised of all ITT subjects who received at least 1 dose of study drug, with analyses according to the treatment actually received.
- The microbiological modified intent-to-treat (m-MITT) population was comprised of all MITT subjects who had a baseline Gram-negative bacterial pathogen.
- The microbiological carbapenem-resistant Enterobacteriaceae modified intent-to-treat (mCRE-MITT) population was comprised of all m-MITT subjects who had a baseline Enterobacteriaceae that was confirmed to be meropenem-resistant.

- The clinically evaluable (CE) population was comprised of all MITT subjects who had no key inclusion or exclusion violations, had sufficient outcome data capture, and received a sufficient number of the expected intravenous doses for a sufficient duration.
- The microbiologically evaluable (ME) population was comprised of subjects who met m-MITT and CE population criteria.
- The carbapenem-resistant Enterobacteriaceae microbiologically evaluable (CRE-ME) population was comprised of subjects who met mCRE-MITT and CE population criteria.
- The pharmacokinetic (PK) population was comprised of all MITT subjects who had at least 1 plasma PK sample drawn.

For Clinical Outcome endpoints, patients with missing data or who were lost to follow-up were to be included in denominators for response rate calculations. Thus, these patients were to be imputed as non-responders.
The planned final sample size for this ongoing trial is approximately 150 total subjects. They will be randomized in a 2:1 ratio such that approximately 100 patients will be in the mer-vab group and approximately 50 subjects will be in the BAT control group.

Reviewers' Comment*: The Applicants' statistical analysis plan states that 'Due to the infeasibility of recruiting a large number of subjects infected with CRE pathogens, no formal power calculations have been performed for this study', and that 'the sample size is based on practical considerations'. It also states that enrollment will be continued until at least 45 subjects (30 mer-vab, 15 BAT) with cUTI or AP are documented to have a baseline CRE organisms and until at least 30 subjects with cIAI (20 meropenem/vaborbactam, 10 BAT) are enrolled, and that 'Once the specified number of subjects are enrolled in the cUTI and/or cIAI indications, data from these subjects may be submitted to regulatory agencies in support of a marketing application, and the enrollment of additional subjects into the specific indication(s) where enrollment was met may be stopped'. However, in this application the data have been submitted despite lower sample sizes (**9** patients with confirmed CRE infection instead of **45** CRE infected patients which was specified for the cUTI cohort).*

Protocol Amendment

The protocol for Study 506 was amended once, before the first subject was enrolled, and the statistical analysis plan was amended once in August 2015 while the study was ongoing. The changes to the statistical analysis plan modified secondary, safety, and exploratory endpoints, clarified certain definitions, and modified the planned tabular presentation of certain results.

Many secondary endpoints were defined in the statistical analysis plan. These endpoints differed for subjects with cUTI/AP, cIAI, HABP/VABP, and BSI, and were predominately defined by considering all-cause mortality and the previously described Clinical Outcome endpoint at various combinations of analysis populations and study visits.

6.2.2. Study Results

This section presents tables and data from interim clinical study report of Study 506.

6.2.2.1. Patient Disposition- Study 506

A total of 41 patients were randomized: 25 to meropenem-vaborbactam and 16 to BAT. Of the 41 patients randomized, 39 received at least one dose of study drug (Safety or MITT Population): 23 in the mer-vab group and 16 in the BAT group. Only 2 randomized subjects did not receive the assigned study drug, and thus were not included in the MITT analysis population. Both were in the meropenem/vaborbactam group and were enrolled in the United States. One of these subjects experienced an adverse event of rash after randomization but prior to dosing that led to study withdrawal, and the Sponsor requested that the other subject not receive study drug because he was on continuous venovenous hemofiltration.

The MITT patients in the mer-vab and BAT groups included 23 patients with cUTI or AP (15 and 8 patients in mer-vab and BAT group respectively), 12 subjects with bacteremia (7 and 5 patients in mer-vab and BAT group respectively), 5 patients with HABP/VABP (3 and 2 patients in mer-vab and BAT group respectively), and 1 patient with cIAI (BAT group only).

Table below displays the disposition of patients in study 506.

Table 56 Patient Disposition by Treatment – (MITT Population- Study 506)

Subject Disposition by Treatment – All Subjects (MITT Population- Study 506)			
	Mer-vab N=23	**BAT N=16**	**Total N=39**
	n (%)	n (%)	n (%)
Subjects who completed study treatment*	15 (65)	11 (69)	26 (67)
Subjects who did not complete study treatment*	8 (35)	5 (31)	13 (33)
Withdrawal by subject	1 (4)	1 (6)	2 (5)
Adverse event	4 (17)	2 (13)	6 (15)
Lack of clinical Improvement	0 (0)	2 (13)	2 (5)
Other**	3 (13)	0 (0)	3 (8)
Subjects who completed the study [π]	15 (65)	13 (81)	28 (72)
Subjects who did not complete the study [π]	8 (35)	3 (19)	11 (28)
Withdrawal by subject	0 (0)	0 (0)	0 (0)
Adverse event	5 (22)	3 (19)	8 (21)
Lost to follow-up	2 (9)	0 (0.0)	2 (5)

Other [£]	1 (4)	0 (0)	1 (3)

Source: Modified from Applicant's Table 4, CSR 506

Percentages are rounded up as follows:
If the digit IMMEDIATELY AFTER the decimal point is 5 or greater, decimal is rounded off to the NEXT NEAREST INTEGER; If the digit IMMEDIATELY AFTER the decimal point is less than 5, decimal is rounded off to the INTEGER BEFORE the decimal point.

*Completed study treatment is defined as completed IV study drug therapy.
**Includes the following patients who did not complete study treatment for the indicated reasons: Patient # 076-005-602 because of a lack of study drug at the site; Patient # 376-003-601 who had a pathogen resistant to mer-vab, and Patient # 840-007-602 who removed his access line.
[π]Completed the study is defined as completed the study through Late Follow-up Visit.
[£]Subject was discharged to a long-term acute care facility and thus, was unable to return for follow-up visits.
BAT = best available therapy; MITT = Modified Intent-to-Treat.

6.2.2.2. Analysis Population - Study 506

Table below displays Analysis Population for study 506.

Overview of Analysis Populations- Study 506		
	Treatment Group	
	Mer-vab N=25	**BAT N=16**
Overall		
ITT Population	25/ 25 (100)	16/ 16 (100)
MITT Population	23/ 25 (92)	16/ 16 (100)
m-MITT Population	17/ 25 (68)	13/ 16 (81)
No Baseline gram-negative bacterial pathogens	6 (26)	3 (19)
mCRE-MITT	15/ 25 (60)	10/ 16 (63)
No Baseline Enterobacteriaceae confirmed to be meropenem-resistant	2 (12)	3 (23)
Safety Population	23/ 25 (92)	16/ 16 (100)
cUTI or AP		
ITT Population	15/ 15 (100)	8/ 8 (100)
MITT Population (Safety Population)	**15/ 15 (100)**	**8/ 8 (100)**
m-MITT Population	10/ 15 (66)	6/ 8 (75)
mCRE-MITT -- (Primary Efficacy Population)	9/ 15 (60)	3/ 8 (38)
Bacteremia		
ITT Population	7/ 7 (100)	5/ 5 (100)
MITT Population	6/ 7 (86)	5/ 5 (100)
m-MITT Population	6/ 7 (86)	5/ 5 (100)
mCRE-MITT [4]	6/ 7 (86)	5/ 5 (100)
Safety Population	6/ 7 (86)	5/ 5 (100)
HABP/VABP		
ITT Population	3/ 3 (100)	2/ 2 (100)
MITT Population	2/ 3 (67)	2/ 2 (100)
m-MITT Population	1/ 3 (33)	1/ 2 (50)

Overview of Analysis Populations- Study 506		
	Treatment Group	
	Mer-vab N=25	BAT N=16
mCRE-MITT	0/ 3 (0)	1/ 2 (50)
Safety Population	2/ 3 (67)	2/ 2 (100)

Source: Modified from Applicants Table 5, CSR 506

AP = acute pyelonephritis; BAT = best available therapy; cUTI = complicated urinary tract infection; HABP = hospital-acquired bacterial pneumonia; ITT = Intent-to-Treat; mCRE-MITT = microbiological carbapenem-resistant Enterobacteriaceae Modified Intent-to-Treat; MITT = Modified Intent-to-Treat; m-MITT = microbiological Modified Intent-to-Treat; VABP = ventilator-acquired bacterial pneumonia.

6.2.2.3. Baseline Demographics Characteristics

Table below displays baseline demographic and other characteristics of study 506 Population.

Table 57 Baseline Characteristics of Safety Population (Study 506)

Baseline Characteristics of Safety Population (Study 506)		
	Treatment group	
	Mer-vab N=23	BAT N=16
Age group (n, %)		
<65 years	10 (43.5)	9 (56.3)
≥65 years	13 (56.5)	7 (43.8)
65-< 75 years	6 (26.1)	2 (12.5)
≥75 years	7 (30.4)	5 (31.3)
Gender		
Male	13 (56.5)	12 (75.0)
Female	10 (43.5)	4 (25.0)
Race (n, %)		
White	21 (91)	13 (81)
Asian	1	1
Black or African	1	2
Region (n, %)		
Europe	17 (74)	8 (50)
North America	5 (22)	7 (44)
Rest of the world	1 (4)	1 (6)
BMI (kg/m2)		
Mean	27	27
CrCl group		
<10 mL/min	0 (0)	0 (0)
≥10 - 19 mL/min	2 (9)	0 (0)
≥20 - 29 mL/min	1 (4)	1 (6)
≥30 - 49 mL/min	4 (17)	5 (31)

Baseline Characteristics of Safety Population (Study 506)		
	Treatment group	
	Mer-vab N=23	**BAT N=16**
≥50 mL/min	15 (65)	9 (56)
Missing	1 (4)	1 (6)
Diabetes status (n, %)		
Yes	8 (35)	7 (44)
No	15 (65)	9 (56)
SIRS status (n, %) [1]		
Yes	8 (35)	8 (50)
No	15 (65)	8 (50)
Immunocompromised		
Yes	5 (22)	8 (50)
No	18 (78)	8 (50)
Charlson comorbidity score (n, %)		
≤2	3(13)	0(0)
3	0(0.0)	2(13)
4	2(9)	1(6)
5	7(30)	4(25)
≥6	11(48)	9(56)
Source: Clinical Reviewers' Analysis		

Reviewers' Comment*: Majority of patients in this study were from Europe, and predominantly white. Mean age was 67 years (range, 33 years to 88 years) in the mer-vab group and 65 years (range, 49 years to 83 years) in the BAT group. Overall, 57% of patients in the mer-vab group and 44% of patients in the BAT group were ≥65 years. The proportions of males were comparatively higher in mer-vab group whereas proportion of females was high in BAT group.*

Only about 35-40% of patients had underlying diabetes mellitus-II. Immunocomprised patients were much lower in mer-vab group as compared to BAT group.

The most frequent risk factor for cUTI or AP in both the mer-vab and BAT groups in the MITT Population was an indwelling urinary catheter (6 of 15 patients and 4 of 8 patients, respectively).

Majority of patients in study 506 had Charlson comorbidity index scores higher than 6 (higher number of underlying comorbid illness). It is surprising that 65% of patients in the mer-vab group did not have systemic inflammatory response syndrome at initial presentation. Majority of patients had CrCl ≥50 mL/min.

6.2.2.4. Baseline Pathogen Characteristics- Study 506

Table below displays the summary of baseline pathogen in Study 506.

Table 58 Summary of baseline pathogens (m-MITT population)-Study 506

Infection Type Baseline Pathogen	Meropenem-Vaborbactam (N= 17) n/N' (%)	Best Available Therapy (N= 13) n/N' (%)	Total (N= 30) n/N' (%)
All subjects			
Klebsiella pneumoniae	15/ 17 (88.2)	9/ 13 (69.2)	24/ 30 (80.0)
Escherichia coli	0/ 17 (0.0)	3/ 13 (23.1)	3/ 30 (10.0)
Enterobacter cloacae species complex	0/ 17 (0.0)	2/ 13 (15.4)	2/ 30 (6.7)
Pseudomonas aeruginosa	2/ 17 (11.8)	0/ 13 (0.0)	2/ 30 (6.7)
Acinetobacter baumannii-calcoaceticus species complex	1/ 17 (5.9)	0/ 13 (0.0)	1/ 30 (3.3)
Proteus mirabilis	0/ 17 (0.0)	1/ 13 (7.7)	1/ 30 (3.3)
Serratia marcescens	0/ 17 (0.0)	1/ 13 (7.7)	1/ 30 (3.3)
Unspeciated coliform	0/ 17 (0.0)	1/ 13 (7.7)	1/ 30 (3.3)
cUTI/AP			
Klebsiella pneumoniae	9/ 10 (90.0)	3/ 6 (50.0)	12/ 16 (75.0)
Enterobacter cloacae species complex	0/ 10 (0.0)	2/ 6 (33.3)	2/ 16 (12.5)
Escherichia coli	0/ 10 (0.0)	2/ 6 (33.3)	2/ 16 (12.5)
Pseudomonas aeruginosa	1/ 10 (10.0)	0/ 6 (0.0)	1/ 16 (6.3)
cIAI			
Escherichia coli	0/ 0	1/ 1 (100.0)	1/ 1 (100.0)
Klebsiella pneumoniae	0/ 0	1/ 1 (100.0)	1/ 1 (100.0)
Proteus mirabilis	0/ 0	1/ 1 (100.0)	1/ 1 (100.0)
Unspeciated coliform	0/ 0	1/ 1 (100.0)	1/ 1 (100.0)
HABP/VABP			
Acinetobacter baumannii-calcoaceticus species complex	1/ 1 (100.0)	0/ 1 (0.0)	1/ 2 (50.0)
Klebsiella pneumoniae	0/ 1 (0.0)	1/ 1 (100.0)	1/ 2 (50.0)
Pseudomonas aeruginosa	1/ 1 (100.0)	0/ 1 (0.0)	1/ 2 (50.0)

Source: Applicants' Table 14.1.4.1. Interim Clinical Study Report 506. (Baseline pathogens were identified based on both local and central laboratories).

Reviewers' Comment*: The predominant pathogen in this trial was K. pneumoniae (15 patients in mer-vab group and 9 patients in BAT groups of the m-MITT population). Among cUTI/AP patients, in the mer-vab group, 9 of 10 patients were infected with K. pneumoniae and 1 patient had cUTI due to P. aeruginosa.*

6.2.2.5. Prior Antibacterial- Study 506

About 60% of patients in the MITT Population had reportedly received prior antibacterial therapy for systemic use within 2 weeks of study enrollment and discontinued before the first

dose of study drug. The most common prior antibacterials were vancomycin, meropenem, and piperacillin/tazobactam.

The initial antibacterials used in the BAT group in m-MITT population were: colistin or polymyxin B (used by 5/13 (38.5%) patients, an aminoglycoside (used by 6/13 (46.2%) patients), ceftazidime-avibactam (used by 1 patient), tigecycline (used by 2/13 (15.4%) patients and a regimen containing a carbapenem were used by 7/13 (53.8%) patients.

Table below displays the type of antibacterial used in BAT control group by individual patients in m-MITT population.

Table 59 Initial BAT regimens (m-MITT population)-Study 506

Initial BAT regimens (m-MITT population)-Study 506						
Subject ID	**Age (years)**	**Gender**	**Country**	**Primary infection type**	**Baseline pathogen**	**Initial BAT regimen**
300-002-602	68	Female	Greece	AP	*E. coli*	Ciprofloxacin 400 mg BID
840-019-601	52	Male	USA	AP	*K. pneumoniae*	Polymyxin B 850,000 q12h
076-003-601	80	Male	Brazil	cUTI	*E. coli*	Colistin 150 mg q12h
376-005-601	64	Male	Israel	cUTI	*K. pneumoniae*	Amikacin 500 mg + meropenem 1g IV q8h
840-006-601	49	Male	USA	cUTI	*E. cloacae*	Gentamicin 360 mg IV q24h
840-010-601	55	Female	USA	cUTI	*E. cloacae* *K. pneumoniae*	Meropenem 1g IV q8h + gentamicin 150 mg IV q24h
376-005-602	81	Male	Israel	BSI	*K. pneumoniae*	Gentamicin 160 mg QD + meropenem 1 g q8h
380-003-601	50	Male	Italy	BSI	*K. pneumoniae*	Meropenem 1.5 g q6h + colistin 4.5 MU q12h + ertapenem 1 g q 24h
380-005-601	53	Female	Italy	BSI	*K. pneumoniae*	Colistin 4.5 MU q12h + tigecycline 100 mg q12h + meropenem 2 g q8h + gentamicin 240 mg q24h
840-006-602	63	Female	USA	BSI	*K. pneumoniae*	Ceftazidime-avibactam 2.5 g q8h
840-010-603	57	Male	USA	BSI	*S. marcescens*	Meropenem 1g IV q8h + ertapenem 1 g IV q24h
840-004-601	67	Male	USA	VABP	*K. pneumoniae*	Colistin 150 mg q12h + gentamicin 500 mg q12h (adjusted for renal function)
826-002-601	75	Male	Great Britain	cIAI	*E. coli* *K. pneumoniae*	Meropenem 1g IV q8h + tigecycline 50 mg q12h
Source: Applicants' Table 12, Interim Clinical Study Report 506.						

Over half the subjects in this trial used concomitant systemic antibacterials on or after the first infusion of study drug. In the MITT population, such therapy was used by 11/23 (47.8%) patients in mer-vab group and 10/16 (62.5%) patients in the BAT group.

6.2.3. Study 506- Efficacy Results

The Applicant has submitted the interim analysis of Study 506 for cUTI/AP subjects. The Efficacy endpoints analyzed included the rates of Cure, Eradication, and overall success at End of Treatment (EOT) and TOC.

All-cause mortality at Day 28

Table 60 Summary of Day 28 all-cause mortality results in Study 506

Summary of Day 28 all-cause mortality results in Study 506				
	Treatment Group			
Subgroup of MITT population	**Mer-vab**	**BAT**	**Difference**	**95% confidence interval**
Entire MITT	(b) (4)			
m-MITT				
mCRE-MITT				
Infection type				
cUTI/AP				
BSI				
HABP/VABP				
cIAI				
Baseline pathogen				
K. pneumoniae				
E. coli				
Enterobacter cloacae species complex				
P. aeruginosa				
A. baumanii				
P. mirabilis				
S. marcescens				
Unspeciated coliform				

Source: FDA Statistical Reviewer
Note: All deaths recorded in this trial occurred at or before Day- 12, except for 1 patient in mer-vab group (mCRE-MITT population) with AP at baseline, who died on Day- 35.

***Reviewers' Comment**: As shown in the table above, in patients with cUTI/AP in the mCRE-MITT population, the Day 28 mortality rates were* (b) (4) *for mer-vab and* (b) (4) *in the BAT group. Unlike Study 505, this trial included patients with carbapenem-resistant infections, and patients in this trial had a greater level of underlying co-morbidities. However, it is difficult to*

interpret the results of this trial due to extremely small sample size, and interim nature of the analysis.

Efficacy Results in Subjects with cUTI or AP

Table below displays Clinical Response, Microbiologic Response, and Overall Response by Pathogen at TOC in Patients with cUTI or AP (m-MITT and mCRE-MITT Populations)-Study 506

Table 61 Clinical Response, Microbiologic Response, and Overall Response by Pathogen at TOC in Patients with cUTI or AP (m-MITT and mCRE-MITT Populations)-Study 506

	m-MITT		mCRE-MITT	
	Mer-vab	BAT	Mer-vab	BAT
	N=10 n (%)	N=6 n (%)	N=9 n (%)	N=3 n (%)
CR-TOC				
Cure	(b) (4)			
Failure				
Indeterminate				
Not Assessed				
MR-TOC				
Eradication				
Persistence				
Recurrence				
Indeterminate				
Overall Success-TOC				
Overall Success				
Overall Success by Pathogen				
Enterobacter cloacae species				
Escherichia coli				
Klebsiella pneumoniae				
Pseudomonas aeruginosa				

Source: Clinical Reviewer Analysis
Indeter= Indeterminate

Reviewers' Comment*: Since the intention of meropenem-vaborbactam development program is to target CRE, it is important to examine the outcomes in patients who were infected with CRE at TOC. Clinical Cures were seen in only 3 of 9 patients in mer-vab and 3 of 3 patients in BAT*

group in the mCRE-MITT Population. At TOC, 4 of 9 patients in the mer-vab group and no patients in the BAT group had clinical outcomes of either Indeterminate or not assessed.

Microbiologic Eradication at TOC occurred in 2 of 9 patients in mer-vab group and 3 of 3 patients in the BAT group in the mCRE-MITT Population.

Overall success at TOC was seen 2 of 9 patients in mer-vab group and 3 of 3 patients in the BAT group in the mCRE-MITT Population. Again at t TOC, 4 of 9 patients in the mer-vab group and no patients in the BAT group had an indeterminate outcome for overall success.
Again, as mentioned before, it is difficult to interpret the results of this trial at this time due to extremely small sample size, and interim nature of the analysis.

On examining the baseline characteristics of cUTI/AP patients in mCRE-MITT population, there was no difference in baseline characteristics or comorbidities (shown in Table below)

Table 62 Characteristics of Patients in mCRE-MITT with cUTI/AP Infection by subject ID, pathogen and Microbiologic Outcome at TOC- Study 506

Characteristics of Patients in mCRE-MITT with cUTI/AP Infection by subject ID, pathogen and Microbiologic Outcome at TOC- Study 506										
USUBJID	***REGION***	***SEX***	***CREATGR***	***CCS***	***DM***	***Age Gr***	***BL-PATHOGEN***	***MR-TOC***	***OR-TOC***	**Treatment group**
300-001-608	*Europe*	*F*	*>=50*	*5*		*65- < 75*	*K. Pneumoniae*	(b) (4)		*Mer-vab*
300-001-609	*Europe*	*F*	*>=50*	*>=6*	***Y***	*65- < 75*	*K. Pneumoniae*			*Mer-vab*
376-003-601	*Europe*	*M*	*>=50*	*5*	***Y****	*< 65*	*K. Pneumoniae*			*Mer-vab*
376-003-602	*Europe*	*M*	*>=30 - 49*	*>=6*	***Y***	*< 65*	*K. Pneumoniae*			*Mer-vab*
300-001-610	*Europe*	*F*	*>=10 - 19*	*5*		*>= 75*	*K. Pneumoniae*			*Mer-vab*
300-001-611	*Europe*	*M*	*>=50*	*>=6*		*< 65*	*K. Pneumoniae*			*Mer-vab*
840-023-601	*North America*	*M*	*N/A*	*4*	***Y***	*< 65*	*K. Pneumoniae*			*Mer-vab*
300-001-602	*Europe*	*F*	*>=50*	*5*		*>= 75*	*K. Pneumoniae*			*Mer-vab*
300-001-605	*Europe*	*F*	*>=20 - 29*	*5*		*>= 75*	*K. Pneumoniae*			*Mer-vab*
840-006-601	*North America*	*M*	*>=50*	*3*		*< 65*	*E. Cloacae Sp. Complex*			*BAT*
506-840-010-601	*North America*	*F*	*>=50*	*5*		*< 65*	*E. Cloacae + K. Pneumoniae*			*BAT*
506-840-	*North*	*M*	*>=30 -*	*>=6*	***Y***	*< 65*	*K. Pneumoniae*			*BAT*

Characteristics of Patients in mCRE-MITT with cUTI/AP Infection by subject ID, pathogen and Microbiologic Outcome at TOC- Study 506										
USUBJID	*REGION*	*SEX*	*CREATGR*	*CCS*	*DM*	*Age Gr*	*BL-PATHOGEN*	*MR-TOC*	*OR-TOC*	Treatment group
019-601	*America*		*49*							
Source: CLINICAL REVIEWERS' ANALYSIS; *Also Immunocompromised; CREATGR=Creatinine Clearance group; CHARGR=Charlson group; AGEGR= Age group; BL-PATH: Baseline Pathogen; CCS – Charlson Comorbidity Index Score; MR-TOC: Microbiologic Response at TOC; DM-II= Diabetes mellitus type-2-yes or No; Erad= Eradication; Indeter=Indeterminate; Succ= Success; Fail=Failure										

Table below summarizes the Baseline Pathogens, Resistance Mechanism, MIC and overall response at TOC for Patients in the Mer-Vab Group (m-MITT Population- Study 506)

Table 63 Baseline Pathogens, Resistance Mechanism, and MIC for Patients in the Mer-vab Group (m-MITT Population- Study 506) - All Infection Types

Baseline Pathogens, Resistance Mechanism, and MIC for Patients in the Mer-vab Group											
No.	Sub	Sex	IFN-TYP	BL-PATH	BETALACT	CARBA	OmpK35	OmpK36	Mer MIC	M/V MIC	OR-TOC
1	300-001-602	F	AP	K. pneumonia	KPC-2 TEM-1 SHV-12	KPC	FS	F	16	≤0.03	(b) (4)
					KPC-2 TEM-2 SHV-12	KPC	FS	GD	>64	1	
2	300-001-605	F	AP	K. pneumonia	KPC-2 TEM-1 SHV-12	KPC	FS	GD	>64	1	
3	300-001-609	F	AP	K. pneumonia	NA	NA	NA	NA	NA	NA	
4	840-023-601	M	cUTI	K. pneumonia	NA	NA	NA	NA	16*	NA	
5	300-001-610	F	AP	K. pneumonia	KPC SHV CTX-M-15	KPC	F	F	64	0.06	
6	376-003-602	M	AP	K. pneumonia	KPC-3 TEM-1 SHV-11	KPC	FS	GD	>64	0.25	
7	376-003-601	M	cUTI	K. pneumonia	SHV-11 NDM-1 CTX-M-15	NDM	FS	F	64	64	
8	300-001-611	M	AP	K. pneumonia	SHV CTX-M-15 OXA-48	OXA-48	FS	GD	64	64	
9	300-001-608	F	cUTI	K. pneumonia	KPC-3 SHV-11	KPC	F	F	32	0.06	
10	300-001-613	M	cUTI	P. aeruginosa	NA	NA	NA	NA	>64	64	
11	076-005-602	F	BACT	K. pneumoniae	KPC TEM SHV	KPC	FS	GD	64	1	

Baseline Pathogens, Resistance Mechanism, and MIC for Patients in the Mer-vab Group

No.	Sub	Sex	IFN-TYP	BL-PATH	BETALACT	CARBA	OmpK35	OmpK36	Mer MIC	M/V MIC	OR-TOC
12	300-001-601	F	BACT	K. pneumoniae	KPC-2 TEM-1 SHV-12	KPC	FS	GD	>64	1	(b) (4)
13	376-001-601	M	BACT	K. pneumoniae	KPC SHV CTX-M-15	KPC	F	F	64	0.25	
14	376-005-603	F	BACT	K. pneumoniae	TEM-11 SHV-11 CTX-M-15 OXA-1 OXA-30	none	F	FS	2	0.5	
15	840-007-602	M	BACT	K. pneumoniae	KPC-2 TEM-1	KPC	F	F	16	≤03	
16	840-018-601	M	BACT	K. pneumoniae	KPC-3 TEM-1 SHV-12 OXA-9	KPC	FS	F	8	≤0.03	
17	300-001-614	M	HABP	A. baumanii-complex	NA	NA	NA	NA	>64	>64	

Source: CLINICAL REVIEWERS' ANALYSIS; IFNTYP: Infection type; BL-PATH= baseline Pathogen; OMP K36=OMP K36-porin amino acid seq OMP K35=OMP K35-porin amino acid seq; F = functional protein; FS = frame-shift leading to inactive protein; GD = insertion of 2 amino acids leading to defective, partially functional protein; HABP = hospital-acquired bacterial pneumonia; KPC = Klebsiella pneumoniae carbapenemase; K. pneumoniae = Klebsiella pneumonia; mCRE-MITT = Microbiological carbapenem-resistant Enterobacteriaceae Modified Intent-to-Treat; MIC = minimum inhibitory concentration; m-MITT = Microbiological Modified Intent-to-Treat; NA = not available; NDM = New Delhi metallo; P. aeruginosa = Pseudomonas aeruginosa.

(b) (4)

Reviewers' Comment: *The table above provides the reader with the overview of baseline pathogen characteristics, underlying mutations, meropenem and meropenem-vaborbactam MIC and overall response at TOC for study 506.*

The efficacy of mer-vab for the treatment of patients with cUTI/AP is difficult to interpret from this interim analysis due to the limitations discussed above.

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7 Integrated Assessment of Effectiveness

Evidentiary Standard

In this submission, the Applicant Rempex Pharmaceuticals achieved the evidentiary standard negotiated with the FDA to support the efficacy and safety of meropenem-vaborbactam for the indication of cUTI including AP.

The efficacy of meropenem-vaborbactam was assessed for the indication of cUTI including pyelonephritis. Rempex Pharmaceuticals had gained an agreement with the FDA that this NDA would be accepted for filing under Section 505(b) (2) of the FD&C Act, for which evaluation of efficacy partially relies on the FDA's previous findings of safety and effectiveness for meropenem. An agreement was also made that the NDA would be accepted for filing on the basis of data from a single, adequately well controlled Phase 3 trial for the proposed indication with safety database of approximately at least 300 subjects treated with proposed dose and treatment duration and supportive safety data from other completed or ongoing trials (Refer to September 30, 2015 FDA meeting minutes). Unmet medical need for complicated urinary tract infections as a serious condition and antimicrobial resistance threat due to KPC-producing carbapenem-resistant Enterobacteriaceae was a key consideration in these meetings. Additionally, according to Title VIII of FDASIA, Generating Antibiotic Incentives Now (GAIN) (which provides incentives for the development of antibacterial and antifungal drugs for human use intended to treat serious and life threatening infections), meropenem-vaborbactam was designated as a qualified infectious disease product ((QIDP) in December 19, 2013.

Study 505 provided statistical evidence that meropenem-vaborbactam is effective for the treatment of complicated urinary tract infections, and is non-inferior to piperacillin/tazobactam.

The assessment of efficacy review for meropenem-vaborbactam was based on a Phase 3, multicenter, randomized, double-blind, noninferiority trial (Study 505) in the treatment of patients with cUTI including AP (please refer to section 6.1 for further details). The primary analysis for this trial (Study 505) was based on evaluation of noninferiority with pre-specified noninferiority margin of -15% for Overall Response at EOIVT visit. There was a statistically significant difference between the mer-vab and pip-tazo Success rates (98.4% and 94.0%, for mer-vab and pip-tazo group respectively). The difference in success rates was 4.5%, and the lower confidence limit of 0.7% for the difference exceeded zero and showed superiority at EOIVT visit.

This application also included interim results from an ongoing Phase 3 trial, Study 506 to provide supportive evidence for the cUTI/AP indication. This study included patients with confirmed or suspected carbapenem-resistant infections including cUTI/AP, HABP/VABP, cAI, or bacteremia (BSI). Patients in this trial had a greater level of underlying co-morbidities. For subjects with cUTI or pyelonephritis at baseline, the primary efficacy endpoint was Overall Success at the TOC visit.

Overall success required both microbiological eradication (baseline pathogens reduced to <10^4 CFU/mL or urine) and a clinical outcome of cure. In cUTI/AP patients, Overall success at TOC was (b) (4) *for mer-vab and* (b) (4) *for BAT comparator in m-MITT population; and* (b) (4) *and* (b) (4) *in mer-vab and BAT comparator group in m-CRE-MITT population.*

For cUTI/AP patients in MITT population, the Day 28 all-cause mortality rates were (b) (4) *for meropenem-vaborbactam and* (b) (4) *in the best available therapy (control) group. However, this trial was non-interpretable due to several statistical limitations including small sample size, planned descriptive analysis, and interim nature of analysis from this ongoing trial. Therefore, Study 506 was not able to provide interpretable or meaningful supportive evidence for either cUTI/AP or for treatment of infections caused by carbapenem-resistant Enterobacteriaceae.*

Clinical Meaning

The treatment for cUTI is antibacterial therapy. Commonly this is initiated intravenously and some patients can be discharged from the hospital and switched to oral antibacterial therapy after several days of successful treatment. Antibacterial treatment for cUTI is typically initiated before the causative pathogen is known, because it can take between 48 to 72 hours to culture a pathogen from a urine or blood sample and determine its susceptibilities. Antibacterial therapy for cUTI is meant to eradicate the bacterial pathogen and thereby prevent the spread of infection and serious complications, and to resolve symptoms associated with cUTI/AP, such as dysuria (painful urination), increased urinary frequency, increased urinary urgency, flank pain, abdominal pain, suprapubic pain, costo-vertebral angle tenderness, nausea, vomiting, fever and chills.

There was a statistically significant difference between the mer-vab and pip-tazo Success rates (98.4% and 94.0%, for the mer-vab and pip-tazo group respectively). The difference in success rates was 4.5%, and the lower confidence limit of 0.7% for the difference exceeded zero and showed superiority at EOIVT visit. Although, Overall Response at the EOIV visit was selected as the primary endpoint for this trial, maintenance of resolution of the core clinical symptoms of cUTI and microbiological eradication few days after the full course of antibacterial treatment is completed (which is TOC visit) is equally important to evaluate the efficacy of an antibacterial drug for cUTI. According to current Agency guidance document on developing antibacterial drugs for the treatment of cUTI, co-primary assessment is recommended to evaluate overall Response at TOC visit. Success rates for this endpoint in Study 505 were lower in both treatment groups as compared to the EOIV endpoint (74.5% and 70.3% in the mer-vab and pip-tazo group respectively) with the lower confidence limit of -4.9% for the treatment effect no longer meeting superiority criteria. Failure rates were similar between the mer-vab and pip-tazo group at TOC (21.4% and 22%). Failure in both groups mainly occurred due to microbiological recurrence.

Additionally, although superiority for the mer-vab at EOIVT was demonstrated, superiority was not reproduced at TOC visit.

Of note, all the failures at EOIVT in the mer-vab group (3 patients) were due to adverse events which were assessed by the investigator as related to study drug. Half of failures at EOIVT in the pip-tazo group (4 of 8 patients) had adverse events, of which two were assessed as not related to study drug. One patient withdrew from the study as they did not want to undergo study procedures, and remaining 3 patients had complicated UTI with pip-tazo resistant baseline pathogens (2 patients with pseudomonas aeruginosa, and 1 patient with K. pneumoniae), with prior therapy failures. These 3 patients were clinical cure or improvement, however were considered failure due to microbiologic persistence or recurrence.

One of the major limitations of this trial was paucity of infection with carbapenem-resistant Enterobacteriaceae (CRE) in Study 505. Majority of pathogens were sensitive to meropenem which limits the evaluation of vaborbactam contribution to the effectiveness of meropenem-vaborbactam in the treatment of cUTI/AP due to CRE infections. Interim data from Study 506 was not interpretable clinically or statistically. Therefore, although in-vitro data suggests effectiveness of mer-vab against certain beta-lactamase producing pathogens (KPC enzyme producing Enterobacteriaceae), it is not possible to comment from clinical trial data on efficacy of mer-vab against CRE pathogens.

Other limitations included limited experience in African American population and in patients with moderate and severe renal failure (CrCl of $\leq$ 30ml/min).

Overall, this application provided reliable evidence that meropenem-vaborbactam is effective for the treatment of cUTI and non-inferior to piperacillin/tazobactam.

In conclusion, the submitted data provides the evidence to support efficacy and safety of meropenem-vaborbactam in the treatment of adult patients with cUTI/AP. Currently there is insufficient clinical data to comment on effectiveness of meropenem-vaborbactam in the treatment of CRE infections.

Communication in Labeling

1. *While we agree with statistical assessment provided by the Applicant and the demonstrated efficacy results of study 505 should be described in the Clinical Studies of the label,* (b) (4)
2. *The trial description should summarize the majority of enrollment (90%) from the Eastern European region and the limited enrollment (2%) from the United States.*

3. *Patients were well balanced across both treatment groups with regard to demographics and other baseline characteristics. However, it should be communicated that the number of patients with CrCl<30 were too few to make any conclusion on therapeutic effect in this subgroup. Additionally a cautionary statement should be added in the label for use in patients with CrCL<30 ml/min. .*

8 Review of Safety

8.1. Safety Review Approach

The safety of IV meropenem-vaborbactam for treatment of cUTI/AP was examined primarily in the safety data from the pivotal Phase3 trial, Study 505, comparing safety profile of meropenem-vaborbactam (mer-vab) versus the safety profile of piperacillin-tazobactam (pip-tazo). Important safety information was also obtained from interim data from ongoing Phase-3 trial, Study 506, and from three Phase 1 clinical trials. These trials were tabulated in Section 5.1.

For the integrated review of safety, in addition to safety data from individual trials, the Applicant has provided two pooled data sets.

-The Phase 3 pool includes Study 505 and Study 506, which provides safety data for all patients treated in the Phase 3 trials. In this pool, the pip-tazo group in Study 505 and the BAT group in Study 506 were pooled into a single comparator group. This pooled data set includes 295 subjects treated with mer-vab and 289 subjects treated with a comparator.

-The All Treated Pool includes all the above-mentioned Phase 1 and Phase 3 trials (Study -501, -503, -504 and Study -505 and -506). Although there are differences in the meropenem-vaborbactam dose, and dosage regimen and study populations (healthy subjects, subjects with varying degrees of renal insufficiency, and patients with different types of infections) across these trials, pooling of all the trials allows for characterization of the overall safety profile for mer-vab. In this pool, the comparators in the Phase 1 trials (placebo, meropenem alone, or vaborbactam alone), and Phase 3 trials (pip-tazo and BAT group), were pooled into a single comparator group. This pooled data set includes 407 subjects treated with varying doses of mer-vab.

Reviewers' Comment*: The Applicant's pooling strategy was discussed during Pre-NDA meeting and the format was agreed by the Agency. The Phase 1 trials were consisted of a heterogeneous population with various doses and durations of mer-vab exposure, therefore, although relevant safety information from those trials are discussed in all treated pool, these trials are not reviewed individually in detail. For detailed review of Phase-1 trials, reader is referred to Clinical Pharmacology review.*

The key adverse events of special interest for meropenem-vaborbactam were identified based on the known safety profile of meropenem, and included pseudomembranous colitis/ *Clostridium difficile*-associated diarrhea (CDAD), hypersensitivity reactions, and seizures. Additionally, since the incidence of heart failure, kidney failure, seizure, and shock reported with meropenem is increased in patients with moderately severe renal impairment (creatinine clearance 10 to 26 mL/min), these events along with other AEs were also examined.

Reviewers' Comment: *Since there were several important characteristics of Study 505 and Study 506 that were different including but not limited to, design of the trial, severity of patients' underlying illness, and comorbidities (Study 506 was open label trial, and had a greater likelihood of enrolling higher risk and critically ill patients with known or suspected CRE infections), analyses from pooled results of Study-505 and 506 should be viewed with these differences in mind. Another important factor affecting the comparability of the pooled data is a different randomization ratio in Study 506, i.e., 2:1 (mer-vab: BAT).*

The incidence of heart failure, kidney failure, seizure, and shock reported with meropenem is increased in patients with moderately severe renal impairment (creatinine clearance 10 to 26 mL/min) However, the pivotal Phase 3 trial, Study 505 excluded patients with CrCl <30ml/min, therefore, it is not possible for this reviewer to comment on the safety of meropenem-vaborbactam in this subgroup.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The overall safety database for meropenem-vaborbactam development program consists of 407 subjects treated with varying doses of meropenem-vaborbactam in five clinical trials: two Phase 3 trials (295 patients) and three Phase 1 trials (112 subjects).
In the Phase1 trials, 112 subjects were treated with mer-vab, including 42 subjects who received the proposed to be marketed dose of mer-vab (meropenem 2 g-vaborbactam 2 g). An additional 70 subjects were treated with vaborbactam alone (10 in Study 501 and 60 in Study 402).
Total of 337 patients (in Phase1 and Phase 3 trials) were exposed to the proposed dose of mer-vab, and 86 subjects were exposed to mer-vab below the proposed dose.

In Phase 3 trials, 545 patients received study treatment in Study 505, including 272 who were treated with the proposed dose of mer-vab (meropenem 2 g-vaborbactam 2 g). In Study 506, 39 patients were treated, and of those, 23 patients received the proposed dose of mer-vab (meropenem 2 g-vaborbactam 2 g).

The following table describes the overall exposure to mer-vab at varying dose during the development program.

Table 64 Safety Database for Meropenem/Vaborbactam Development Program

Trial	Indication	mer-vab 2g-2g	mer-vab any dose*	pip-tazo	BAT	Placebo	Total
Phase 3 Trials							
505	Controlled trial conducted for cUTI/AP	272	0	273	N/A	N/A	545
506	Selected serious infections due to known or suspected CRE [π]	23	0	N/A	16	N/A	39
Phase 1 Trials							
501	Safety and PK in HV	16	45	N/A	N/A	18	94
503	HV PK Epithelial Lining Fluid	26	0	N/A	N/A	N/A	26
504	HV and subjects with RI	0	41	N/A	N/A	N/A	41
						Total Safety Pool	**745**

Source: Clinical Reviewers' Analysis;
Total Overall Exposure proposed dose: n=337; Total Overall exposure other than proposed dose (all lower than proposed): n =86
mer-vab: meropenem/Vaborbactam; pip-tazo: Piperacillin/Tazobactam; BAT: Best Available Therapy; HV: Healthy Volunteer
*mer-vab dose lower than the proposed dose of 2g-2g;
π cUTI /AP, cIAI, HABP,VABP, and bacteremia;

In study 505, patients were required to have an illness severe enough to warrant the use of IV antibacterial for at least 5 days. The patients could subsequently be switched to oral levofloxacin (500 mg q24h) or alternative oral antibacterial in case of levofloxacin resistance , after a minimum of 15 doses of IV therapy if, pre-specified criteria were met to complete a total treatment course (IV plus oral) of 10 days. Subsequent two tables below summarize the duration of exposure to study drugs in safety population in Study 505, and overall extent of study drug exposure in Pooled trials.

Table 65 Duration of Exposure in Study 505 (MITT)

	mer-vab N=272 n (%)	**pip-tazo N=273 n (%)**	**Total N=545 n (%)**
IV Study Drug Exposure (in days)- Study 505			
<5 days	13 (5)	17 (6)	30 (5.5)
>=5 - <7 days	96 (35)	91 (33)	187 (34)
>=7 - <10 days	69 (25)	69 (25)	138 (25)
10-11 days	91 (33)	91 (33)	182 (33)
>11 days	3 (1)	5 (2)	8 (1.5)
	mer-vab	**pip-tazo**	**Total**
Mean duration of IV Treatment (days)	8	8	8
Source: Clinical Reviewers' Analysis			

Table 66 Overall Extent of Study drug Exposure (Pooled Trials)

Comparison of Key Exposure Parameters for Pooled (Safety Population)				
	Phase 3 Pool		**All Treated Pool**	
	M/V (N=295)	Comparators (N=289)	M/V (N=407)	Comparators (N=338)
	n (%)	n (%)	n (%)	n (%)
Overall extent of exposure (days) *				
Mean (SD)	10.1 (2)	9.9 (2)	8.9 (4)	10.3 (3)
Exposure to IV therapy (days)				
Mean (SD)	8.1 (3)	8.0 (3)	7.5 (4)	8.8 (3)
Exposure to IV therapy category, n (%)				
≥1 - <5 days	17 (6)	19 (7)	85 (21)	19 (6)
≥5 - <7 days	97 (33)	94 (32.5)	97 (24)	94 (28)
≥7 - <10 days	78 (26)	74 (26)	86 (21)	80 (24)
10 - 11 days	93 (31.5)	91 (31.5)	93 (23)	92 (27)
>11 days	10 (3)	11 (4)	46 (11)	53 (16)

Source: Table-13, Integrated Summary of Safety 5.3.5.3
M/V: meropenem/vaborbactam
*Overall Extent of Exposure includes IV therapy and oral step-down therapy.
Phase III Pool: Studies 505 and 506 pooled;
All Treated Pool: Includes all subjects (healthy volunteers and patients) treated with Meropenem-vaborbactam or comparators given in parallel with Meropenem-vaborbactam;
Exposure = last dose date of study drug – first dose date of study drug + 1
IV=intravenous; SD=standard deviation;

Reviewers' Comment*: Overall extent of exposure was adequate to evaluate the use of meropenem-vaborbactam for indication of cUTI/AP. Although, pooling data from different trials can improve the precision of an incidence estimate (i.e., narrow the confidence intervals by enlarging the sample size) of rare events. Pooling of observations assume exchangeability of subjects who had similar characteristics and were given comparable care across trials. In this case, analyses should be viewed with caution because there are several important characteristics of Study 505 and Study 506 that differ, and it is possible that different populations may have different vulnerabilities to the study drug, and therefore, different risk profiles. For example, Study 506 was an open-label, and more likely to enroll higher risk patients with CRE infections, whereas, Phase 1 trials included healthy volunteers, and one Phase 1 trial, Study 504, included patients with varying degrees of renal insufficiency.*

8.2.2. Relevant characteristics of the safety population:

Characteristics of patients in pooled Phase 3 trials and all treated pools are presented in the Table 67 below. In the Phase 3 Pool, demographic characteristics were similar in the mer-vab and comparator groups. The majority of patients in both mer-vab and the comparator groups were female (65% and 64%, respectively), and white (93% and 92% respectively). Mean age was 54 years in the mer-vab and 53 years in the comparator group. Most patients were <65 years of age (66% and 62%, respectively). Mean BMI was 27 kg/m^2 in mer-vab group and 26 kg/m^2 in the comparator group. Demographic characteristics of the two treatment groups were also similar in the All Treated Pool.

Table 67 Demographic Characteristics of Safety Population in Pooled Trials

	Phase 3 Pool		All Treated Pool	
Category	**M/V (N=295) n (%)**	**Comparators (N=289) n (%)**	**M/V (N=407) n (%)**	**Comparators (N=338) n (%)**
Age (years)				
N	295	289	407	338
Mean (SD)	54 (19)	53 (21)	50 (20)	49 (22)
Age (years)				
<65	195 (66)	179 (62)	298 (73)	228 (67)
≥65	100 (34)	110 (38)	109 (27)	110 (33)
65 - <75	54 (18)	59 (20)	63 (16)	59 (18)
≥75	46 (16)	51 (18)	46 (11)	51 (15)
Gender, n (%)				
Male	104 (35)	105 (36)	182 (45)	139 (41)
Female	191 (65)	184 (64)	225 (55)	199 (59)
Race, n (%)				
White	275 (93)	265 (92)	360 (89)	310 (92)
Non-White *	20 (7)	24 (8)	47 (12)	28 (8)
Region, n (%)				
North America	13 (5)	16 (6)	80 (20)	16 (5)
Europe	261 (88)	251 (87)	261 (64)	251 (74)
Asia Pacific **	4 (1)	5 (2)	4 (1)	5 (1.5)
Rest of World	17 (6)	17 (6)	62 (15)	66 (20)
Weight (kg)				
N	295	288	407	337
Mean (SD)	75 (19)	72 (18)	77 (19)	73 (17)
BMI				
N	294	288	406	337
Mean (SD)	27 (6)	26 (6)	27 (6)	26 (6)

Source: ISS Table- 11
M/V= meropenem-vaborbactam; BMI=Body mass index (kg/m2); N= Number
* Non-White includes Asian, American Indian or Alaska Native, Black or African-American, Native Hawaiian or Aboriginal/Torres Strait Islander or Other Pacific Islander, and Other
** Asia-Pacific is combined with Rest of World will be combined for the subgroup analyses
Phase III Pool: Studies 505 and 506 pooled; All Treated Pool: Includes all subjects (healthy volunteers and patients) treated with Meropenem-vaborbactam or comparators given in parallel with Meropenem-vaborbactam; SD=standard deviation

***Reviewers' Comment**: The treatment arms appeared well balanced with respect to age, gender, race, ethnicity, BMI, enrollment region. Similarly demographic characteristics and baseline disease status, including Charlson comorbidity index, diabetic status, SIRS and infection type were similar between treatment arms in Study 505.*

Other important baseline characteristics of Study 505 and Study 506 is presented sidewise for comparison for better understanding of the difference in patient characteristics between the two trials which will help make the better assessments when safety is reviewed in the Pooled Phase 3 trials.

Patients were similar between the mer-vab and comparator in both trials with respect to baseline creatinine clearance, diabetes status, systemic inflammatory response syndrome (SIRS), and Charlson comorbidity score. Study 505 and 506 are displayed sidewise for comparison.

Table 68 Other Baseline Characteristics of Study 505 and 506 (Phase 3 Safety Population)

	Study 505		**Study 506**	
	Mer-vab N-272	Pip-tazo N=273	Mer-vab N-23	BAT N=16
Categories	n (%)	n (%)	n (%)	n (%)
CrCl-group (ml/min)				
Missing	4 (1.5)	3 (1)	1 (4)	1 (6)
<30 ¥	2 (1)	2 (1)	3 (13)	1 (6)
30 - 50	29 (11)	35 (13)	4 (17)	5 (31)
>50	237 (87)	233 (85)	15 (65)	9 (56)
Diabetes status				
No	230 (85)	229 (84)	15 (65)	9 (56)
Yes	42 (15)	44 (16)	8 (35)	7 (44)
Presence of SIRS*				
No	195 (72)	183 (67)	15 (65)	8 (50)
Yes	77 (28)	90 (33)	8 (35)	8 (50)
Charlson Score**				
0	70 (26)	82 (30)	0 (0)	1 (4)
1	22 (8)	22 (8)	0 (0)	1 (4)
2	37 (14)	22 (8)	0 (0)	1 (4)
3	48 (18)	40 (15)	2 (13)	0 (0)
4	32 (12)	32 (12)	1 (6)	2 (9)
5	31 (11)	30 (11)	4 (25)	7 (30)
6	16 (6)	24 (9)	2 (13)	2 (9)
7	5 (2)	8 (3)	2 (13)	3 (13)
8	7 (3)	7 (3)	1 (7)	0 (0)
9	1 (0.4)	5 (2)	2 (13)	4 (17)
10	3 (1)	1 (0.4)		1 (4)
Bacteremia at baseline			**Subjects with Diagnosis of Bacteremia**	
No	241 (89)	243 (89)	0	0
Missing	19 (7)	15 (5.5)	0	0
Yes	12 (4)	15 (5)	6 (26)	5 (31)
Prior Therapy Failure				
No	269 (99)	266 (97)	18 (78)	16 (100)
Yes	3 (11)	7 (3)	5 (22)	0
Infection Type			**Infection Type in cUTI/AP category**	

	Mer-vab (N=272) n (%)	Pip-tazo (N=273) n (%)	Mer-vab (N=15) n (%)	BAT (N=8) n (%)
Acute Pyelonephritis	161 (59)	161 (59)	8 (53)	3 (37.5)
cUTI	111 (41)	112 (41)	7 (47)	5 (62.5)

Source: Clinical Reviewers' Analysis.

AP= Acute Pyelonephritis
¥ CrCl= Creatinine Clearance; CrCl was an exclusion criteria in Study 505, but there are 2 patients in each treatment arm with CrCl<30.
**Charlson score (Charlson et al, J. Chron Dis 1987) was used to assess co-morbid conditions to determine relative risk of mortality based on the score is as follows: 0—RR 1.2-1.5 ; 1—RR 1.5-2.5
2—RR 2.5-3.5 ; 3—RR 3.5-4.5; 6—RR > 6

***Reviewers' Comment**: The demographic characteristics of patients in the mer-vab and comparator groups were similar in both Study 505 and Study 506. When comparing the total patient population between the two studies, the majority of patients in both trials were White, and <65 years of age. BMI was also comparable between the two studies. However, proportions of females were higher in Study 505 (66%), whereas male predominated in Study 506 (64%). Majority of enrollment was from Europe in both trials, however, patient enrollment from North America were higher in Study 506 as compared to Study 505 (31% vs 3%). Only about 15% of patients were diabetic in Study 505, whereas, almost half were diabetic in Study 506. Majority of patients had CrCl >50 ml/min in both studies. About 40% of patients presented with SIRS in Study 506 compared to 30% in Study 505. As predicted, comorbidity index was higher in Study 506 compared to Study 505. About 50% of patients in Study 505 had Charlson comorbidity score of <=3 whereas, almost 50% in Study 506 had Charlson comorbidity score of >=6.*

(b) (4)

they excluded patients with severe renal impairment from Study 505, because efficacy and safety data using the modified proposed dose should have been gathered for this important subgroup. Because these data were not collected, it is not possible to comment on this group of patients with severe renal insufficiency. The Applicant has included this sub group in Study 506; however, interim data is not sufficient for analyses. Since urinary tract abnormalities, catheterizations, and obstruction to the urinary tract are causal factors for cUTI, renal impairment is anticipated in large number of patients in this disease population in clinical settings.

Overall, demographics of the patient populations were comparable and balanced between two treatment arms in both Phase 3 trials. The range of underlying comorbidities in the safety population represents that encountered in clinical practice in U.S. population with the exception

of black population which is not well represented in the mer-vab trials, and other exceptions mentioned above.

8.2.3. Adequacy of the safety database:

***Reviewers' Comment**: The safety database for meropenem-vaborbactam is adequate to assess the safety of the drug for cUTI/AP indication, given the known safety profile of meropenem. The Applicant has discussed the size of the safety data base with the FDA during clinical development. The safety database includes recommended minimum of approximately 300 patients exposed to intended dose of meropenem-vaborbactam. Most of the baseline demographics, clinical characteristics, underlying comorbidities, and baseline disease status appeared comparable among the two treatment groups. The Applicant's safety analysis plan was found to be acceptable with an appropriate focus on the anticipated safety issues with meropenem-vaborbactam. The definitions of AEs and method of obtaining descriptive statistics was standard and acceptable. The plasma clearance and elimination half-life for meropenem is 10.5 L/h and 2.3 hours, respectively, and vaborbactam is 8.0 L/h and 2.2 hours, respectively, therefore the time period of TEAEs defined as to the end of the study visits (Day 22-26) was appropriate and would be anticipated to cover the period of anticipated side-effects.*
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8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant submitted all required data. The trial was conducted in accordance with the draft Guidance document and as delineated in the original protocol.
All other issues related to Data quality and integrity is discussed in section 6.1.11.1 -Data Quality and Integrity – Reviewers' Assessment.

8.3.2. Categorization of Adverse Events

No significant issues were identified with respect to recording, coding, and categorizing AEs. The Applicant categorized AEs and SAEs in accordance with standard regulatory definitions. For reference, some key elements are reproduced briefly below.
All adverse events, including observed or volunteered problems, complaints, or symptoms, were recorded and entered on the appropriate eCRF. Adverse events were coded using the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA) available, version 15.0.

AEs were graded using the National Cancer Institute-Common Terminology Criteria for AEs (NCI CTCAE) 5-point (Grade 1, 2, 3, 4, and 5) grading scale (version 4.0). AEs not listed in the NCI-CTCAE grading system were graded as follows:

- Grade 1 - Mild: asymptomatic or mild symptoms OR clinical or diagnostic observations only OR intervention not indicated
- Grade 2 -Moderate: minimal, local or noninvasive intervention indicated OR limiting age appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- Grade 3 - Severe or medically significant, but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated OR disabling OR limiting self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, not being bedridden)
- Grade 4 - Life-threatening consequences: urgent intervention indicated
- Grade 5 - Death related to AE

Causality Assessment

The relationship of each adverse event will be assessed using the following definitions:

Not related

- Event occurring before dosing.
- Event or intercurrent illness due wholly to factors other than drug treatment.

Unlikely

- Poor temporal relationship with drug treatment.
- Event easily explained by subject's clinical state or other factors.

Possible

- Reasonable temporal relationship with drug treatment.
- Event could be explained by subject's clinical state or other factors.

Probable

- Reasonable temporal relationship with drug treatment.
- Likely to be known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot easily be explained by subject's clinical state or other factors.
-

Treatment-Emergent Adverse Events (TEAEs)

Treatment-emergent adverse events (TEAEs), which include clinical laboratory test variables that are reported as adverse events, were monitored and documented from the first dose of study drug until the completion of study participation. TEAE of Special Interest was identified based on identified risks for meropenem alone:

- Hypersensitivity, identified with a combination of Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs)

- Seizure, identified with the SMQ of convulsions
- Pseudomembranous colitis/CDAD, identified with the SMQ of Pseudomembranous colitis

Reviewers' Comment*: The analysis of AEs performed by the applicant is considered adequate. This clinical reviewer also performed independent analysis of AEs in a similar way: by SOC (System Organ Class) and by PT (Preferred Term). For analysis of SOCs, the number of subjects with even one TEAE in that SOC was counted, while within each SOC, the number of events were counted separately. Thus, one subject may have had more than one TEAE in the same SOC.*

8.3.3. Routine Clinical Tests

A complete physical examination was recorded at screening. A limited, symptom-based, physical examination was performed at other indicated visits. If a subject did not display symptoms, no limited physical examinations were performed. Systolic and diastolic blood pressures, pulse, and respiratory rate were measured in all of the studies. ECG data, including PR interval, QRS duration, and QT interval, were collected in all of the studies. ECG data is discussed in section 8.4.8 of this review.
The routine clinical laboratory assessments included hematology, clinical chemistry (ALT, AST, total bilirubin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), calcium, creatine phosphokinase (CPK), creatinine, glucose, potassium, and sodium), and Urinalysis.

Reviewers' Comment*: Routine clinical testing of patients enrolled in a trial, includes efforts to elicit adverse event data by monitoring laboratory tests, vital signs etc. The schedule of laboratory testing was acceptable overall, based on the expected safety issues with meropenem.*

8.4. Safety Results

The table below displays the high level overview of mer-vab safety results in Phase-3 trials, Study 505 and Study 506 sidewise for comparison.

Table 69 Safety Overview: Study -505 and Study 506 (Safety Populations)

	Study -505 Safety Population		Study 506 Safety Population	
	Mer-vab N=272	Pip-Tazo N=273	Mer-vab N=23	BAT N=16
	N (%)	N (%)	N (%)	N (%)
Deaths	2 (0.73)	2 (0.73)	5 (22)	3 (19)
SAEs	11 (4)	12 (4.4)	9 (39)	6 (37.5)
SAE Related	1 (0.4)	1 (0.4)	0 (0)	2 (12.5)
D/C study drug d/t SAE	3 (1)	5 (2)	4 (17)	1 (6)
ALL TEAEs	106 (39)	97 (35.5)	20 (87)	14 (87.5)
D/C study drug d/t TEAE	7 (2.6)	14** (5)	3 (13)	2 (12.5)
TEAE Related to study drug	41 (15)	35 (13)	6 (26)	9 (56)**
TEAE mild	49 (18)	45 (16.5)	5 (22)	3 (19)
TEAE mod	45 (16.5)	37 (13.6)	3(13)	2 (12.5)
TEAE severe	7 (2.6)	13 (5)	5 (22)	6 (37.5)

Source: Clinical Reviewers' Analysis

D/C= Discontinuation; d/t= due to; BAT – best available therapy

***Reviewers' Comment**: The high-level safety overview and general comparison to pip-tazo or BAT suggests that mer-vab has a relatively favorable safety profile. The rates of TEAEs in Study 506 are more than twice the rates of TEAEs in Study 505. The number of deaths was also higher in Study 506 due to severity of illness in this study population. The rate of TEAEs related to study drug was higher in the BAT arm in Study 506 and the rate of discontinuation of study drug due to TEAEs was higher in the pip-tazo arm. Detailed safety analyses are discussed below.*

The safety analysis population set, MITT was used for all analyses unless otherwise specified; all subjects who received at least one dose of study medication were included in the MITT.

8.4.1. Deaths

There were total of 12 deaths reported in the mer-vab development program. All deaths were reported in the Phase-3 trials (7 (2.4%) patients in the mer-vab group and 5 (1.7%) patients in the comparator group). Majority of deaths occurred in Study 506. Four of the 12 deaths occurred in Study-505 (2 each in the mer-vab and pip-tazo group), and the rest of 8 fatalities occurred in Study-506 (5 patients in the mer-vab group and 3 patients in the pip-tazo group). No deaths were considered to be related to the study drugs by the Applicant.

***Reviewers' Comment**: Patient deaths were evaluated by reading the CSR, and perusing the eCRF for each patient. In addition, the demographic information provided by the Applicant in the individual study CSRs was perused for medical and surgical background. This reviewer noticed that none of the deaths were categorized as a clinical outcome of 'Failure' by the Applicant. Information request was sent to the Applicant for clarifications (reader is referred to' Data Quality and Integrity Assessment' section 6.1.11 for detail).*

The largest concentration of deaths was in Europe (which was also the highest enrolling region) where 4 deaths (3 in the mer-vab group and, 1 in the comparator group) occurred at Site 300-001, 2 deaths (1 in each mer-vab and pip-tazo group) at site 376-005 and remaining 3 deaths (2 in the mer-vab group and 1 in BAT group) occurred in North America and Rest of the World. Most deaths occurred in patients older than 70 years of age. Only 2 deaths occurred in patients 65 years or younger, of which the youngest was 61 years old. All deaths that occurred in the mer-vab development program by subject-ID are briefly summarized in table below.

Fatal AEs that occurred in more than 1 subject included sepsis or septic shock (2 patients in mer-vab group and 3 patients in pip-tazo group). None of the deaths was directly attributed to either study drug (mer-vab or comparator), and events were consistent with the severity of patient's illness.

As mentioned earlier, Study 506 enrolled patients infected with Carbapenem Resistant Enterobacteriaceae with higher degree of disease severity; therefore these accounts of patient deaths should be interpreted in context a serious infection with a real possibility of morbidity and death, even if ideally managed with best available therapy.

Table below summarize the list of death by subject-IDs, day of death in relation to study day, and cause of death.

Table 70 Deaths in Meropenem-Vaborbactam Development Program

Subject ID/ Demographics	Age/Race/ Sex	Infection Type	Cause of death (MedDRA PT)	Days of IV therapy	Study Day of death	Relationship to Study Drug
Study-505: mer-vab						
076-003-510	76/W/M	cUTI	Aspiration	9	14	Not related
203-002-503	74/W/M	cUTI	Sudden cardiac death	8	11	Not related
Study 505: pip-tazo						
300-001-514	86/W/F	AP	Septic shock	2	2	Not related
703-005-509	81/W/F	AP	Pulmonary Embolism	2	3	Not related
Study-506: mer-vab						
300-001-601	69/W/F	Bacteremia (Known CRE)	Cardiac Arrest	3	4	Not related

Subject ID/ Demographics	Age/Race/ Sex	Infection Type	Cause of death (MedDRA PT)	Days of IV therapy	Study Day of death	Relationship to Study Drug
300-001-609	65/W/F	AP (Known CRE)	Septic Shock	8	35	Not related
300-001-610	88/W/F	AP (Known CRE)	Sepsis	3	4	Not related
376-005-603	74/W/F	Bacteremia (Known CRE)	Shock hemorrhagic	4	5	Not related
840-019-603	61/W/M	cUTI (Known CRE)	Multi-organ failure	12	12	Unlikely related
Study-506: Comparator						
376-005-602	81/W/M	Bacteremia (Known CRE)	Sepsis	2	3	Not related
840-004-601	67/W/M	VABP (Known CRE)	Septic Shock	6	12	Not related
826-002-601	75/Asian/M	c IAI (Known CRE)	Septic Shock	3	11	Not related
Source: Clinical Reviewers' Analysis, and ISS						

***Reviewers' Comment**: Most common cause of death was septic shock, which occurred in 1 patient [0.3%] in mer-vab group and 3 patients [1%] in the comparator group; followed by sepsis, 1 [0.3%] patient in each treatment group. As per the investigator assessment, none of the deaths was attributed to either study drugs and all events were considered as related to the severity of the patients' illness, progression of disease or underlying comorbid conditions.*

The main features of patients who died in mer-vab arm are summarized in table below.

Table 71 Tabulated Narratives of Deaths in the Meropenem-Vaborbactam group (Phase 3 Trials)

#	Study/ Demographics/Infection type	Clinical Details	Reviewer's Assessment
Study 505 (cUTI/AP study)			
1	505-076-003-510 76/W/M/	PMH: COPD with recent respiratory failure (tracheostomy, on Bi-PAP); alcoholic hepatitis, bilateral pleural effusions, BPH, SVTs, arrhythmias,	*This patient had a poorly compensated COPD and death was most probably related to the aspiration pneumonia and*

#	Study/ Demographics/Infection type	Clinical Details	Reviewer's Assessment
	cUTI Aspiration on Study Day 14	gastritis, and abdominal distension Course: Completed 10 days of IV study drug Tx with Clinical outcome of 'Improvement' on study D- 9. On study D-13, patient experienced abdominal distension, gastric stasis, nausea and vomiting with altered level of consciousness. Died on D-14.	*resultant respiratory failure. This reviewer agrees with the investigator's assessment of causation of death as not related to study drug.*
2	505-203-002-503 74/W/M/ cUTI Cardiac Arrest on Study Day 11	PMH: Quadriplegia, hypospadias, esophageal achalasia, biliary obstruction, ischemic proctocolitis, monoclonal gammopathy, nicotine and alcohol use. Course: On D-1, had a dilation of urethra, and trans-urethral resection due to urethral stricture. Completed IV study Tx on D-8, and switched to oral step down (levofloxacin); then transferred to neurology department on D-8 for planned investigation into progressive quadriparesis with suspected MND and ALS .On D-11, had a sudden loss of consciousness secondary to circulatory and respiratory arrest. Autopsy was not done.	*Complicated UTI was improving on study drug and the patient had completed 10 days of study therapy. Although, a specific cause of death could not be assigned, the death of this patient with progressing quadriparesis of uncertain etiology does not seem to be related to study drug.* *This reviewer agrees with the investigator's assessment.*
Study 506 (Study on known or suspected CRE)			
1	506-300-001-601 69/W/F cUTI Cardiac Arrest D-4	PMH: DM-II, seizures, recent h/o status epilepticus 2 months prior to enrollment, HTN, dementia, psychotic depression, aspiration PNA, hypoalbuminemia, hypocalcemia, hypomagnesemia, and decubitus ulceration. Course: Known CRE (bacteremia with *K. pneumoniae*), with failure to thrive, hypotension, decubitus ulcer and aspiration pneumonia. Was improving clinically until D-3. On D-4, had a sudden	*This patient with baseline poor performance status, status epilepticus, aspiration pneumonia and bacteremia due to MDR strain of Klebsiella pneumoniae most likely died as a consequence of the progression of the disease. However, meropenem by itself is known to cause or worsen the seizures. This patient had a history of seizures and status*

#	Study/ Demographics/Infection type	Clinical Details	Reviewer's Assessment
		cardiac arrest. EKGs reportedly not abnormal prior to event.	*epilepticus (although no active treatment for seizure was listed). Possibility of worsening of seizures or status epilepticus cannot be excluded. Autopsy was not performed. No additional details were available. An association with the study drug cannot be definitively excluded here. Causality assessment is difficult in this significantly ill population.*
2	506-300-001-609 65/W/F AP (Known CRE) Septic Shock D- 17	PMH: DM-II, HTN, Cushing's disease, COPD, rheumatoid arthritis, AKI, and diarrhea. Course: Was treated with study drug until D-8, EOT assessment performed on D-8, and evaluated as clinical cure, discharged home. On D-17 (TOC) readmitted, assessed as 'Indeterminate'. Was tachycardic (120), tachypneic (RR-25) with BP of 80/50 mmHg. CXR revealed a density in the left lower lung. Laboratory studies revealed leukocytosis (WBC of 15,250 mm3), Cr 1.7 mg/dL and CRP of 312 mg/dL. Started on Tx with meropenem, colistin, linezolid, oseltamivir, gentamycin, hydrocortisone, for infection suspected to be of respiratory origin. On D-29, condition worsened, had cardiopulmonary arrest.	*Patient was readmitted with septic shock. This patient's death was most likely due to disease progression leading to septic shock and therapy failure so this death could be potentially related to the lack of efficacy of study drug.* *Of note, the Applicant has assessed this patients' TOC Outcome as – 'Indeterminate'.*

#	Study/ Demographics/Infection type	Clinical Details	Reviewer's Assessment
3	506-300-001-61088/W/F AP (Known CRE) Sepsis D-4	PMH: CAD, CHF, hypothyroidism, MI, HTN, extrapyramidal dystonia, cholecystectomy, LBB, decubitus ulcer, RTI, and aspiration PNA. Course: Completed 5 doses of IV study drug by D-3. On night of D-3, found lethargic, with tachypnea, tachycardia, started on supportive measures. On early AM of D-4, found apneic with ECG reveling cardiac arrest.	*This reviewer agrees with investigator's assessment of death as cardiac arrest related to septic shock due to the disease progression. However, given that the death occurred only after 5 doses of study drug, it may not be attributed to low efficacy of study drug.* *There was no evidence of cardiac toxicity during treatment based on reported AEs, laboratory results, vital signs, and ECG results.*
4	506-376-005-60374/W/F Bacteremia (Known CRE) Shock hemorrhagic D-4	PMH: PE, on mechanical ventilation, severe anemia , paroxysmal AF, CHF, DM-II, HTN, obesity, thrombocytopenia, ARDS, DIC, CRF on HD, left lung pneumothorax, bronchospasm, hyperlipidemia, CVA, rectal bleeding. Course: Admitted with PE prior to enrollment. Received IV study drug until D-4, subsequently that evening had a massive GI bleeding and hypotension. While getting stabilized, experienced another bout of rectal bleeding and shock. The patient died on D-5.	*This reviewer agrees with the investigator's causality assessment.* *Massive GI bleeding related to heparin causing hemorrhagic shock.*
5	506-840-019-60361/W/M cUTI (Known CRE) MOF D-12	PMH: HTN, h/o bacterial endocarditis, CHF, intracranial septic embolism, splenic infarction, DM-II, Severe MR, intracranial bleed, hemiplegia, septic and cardiogenic shock. Course: Admitted with MOF and cUTI with known CRE. Received study drug until D-6 without any improvement. On D-6, "worsening multiorgan failure" of unknown etiology. On D-7, study drug	*This reviewer agrees with the Investigators causality assessment as 'septic shock' with multiorgan failure.* *As to the relation to study drug, this patients' worsening of multiorgan failure was most likely related to progression of the disease and therefore, patient's death could be*

#	Study/ Demographics/Infection type	Clinical Details	Reviewer's Assessment
		was permanently discontinued and additional treatment with vancomycin, micafungin, and pip-tazo started. Transferred to palliative care. On D-12, withdrawn from the study and died.	*potentially related to the lack of efficacy of study drug.*

Source: e-CRF, ISS;
D= study day; Tx= Treatment; h/o= history of; d/c ed= discontinued; MND= motor neurone disease; ALS=amyotrophic lateral sclerosis; DM-II= diabetes mellitus type-2; PNA= Pneumonia; RTI= Respiratory tract infection; PE= Pulmonary embolism; ARDS=Acute Respiratory Distress Syndrome; DIC=Disseminated Intravascular Coagulation; MR= Mitral Regurgitation; MOF= Multiorgan Failure;
COPD= Chronic obstructive pulmonary disease; HTN= hypertension; BPH= Benign prostatic hypertrophy, SVTs= Supraventricular tachycardia; Hgeic= Hemorrhagic

Reviewers' Comment*: Overall, I agree with the investigators' assessments on these deaths. The subjects' underlying co-morbidities, especially cardiac and respiratory diseases, and old age in most of the cases, could have contributed to these deaths. Yet, lack of efficacy of study drug could have contributed to the outcome of death, at least in the cases of multi-organ failure, sepsis and septic shock. However, additional comorbidities are confounding factors that make the assessment of causality of these deaths difficult. All these deaths were assessed as 'Indeterminate', in the primary analysis of efficacy.*

8.4.2. Serious Adverse Events

The incidence of any SAEs was similar between the mer-vab and comparator groups in Study 505, Phase 3 Pool and All treated Pool (Table below).

There were 11 (4.0%), and 12 (4.4%) patients in the mer-vab group and comparator group, respectively, with any SAEs in Study 505; and 20 (6.8%) and 18 (6.2%) patients in the mer-vab group and comparator group with any SAEs in Phase 3 Pool. All SAEs occurred in Phase 3 trials except for 2 SAEs in Phase 1 trial (Study-504, Renal Impairment study).

In Study 505, no SAE was reported by more than 1 patient in either group. Two patients in each group had fatal SAEs, including Patient # 076-003-510 with aspiration pneumonia, and patients # 203-002-503 with sudden cardiac death in the mer-vab group; and patient # 300-001-514 with septic shock and patient # 703-005-509 with a pulmonary embolism in the pip-tazo group.

Table below displays SAEs occurred in Study 505.

Table 72 Serious Adverse Events (Safety Population- Study 505)

System Organ Class **Preferred Term**	**Mer-vab** **N=272**	**Comparator** **N=273**
Number of subjects with at least one SAE	11(4.0)	12(4.4)
Cardiac disorders	**1 (0.4)**	**0 (0)**
Cardiac failure congestive	1 (0.4)	0 (0)
General disorders and administration site conditions	**1 (0.4)**	**0 (0)**
Sudden cardiac death*	1 (0.4)**	0 (0)
Infections and infestations	**2 (0.7)**	**7 (2.6)**
Bacterial sepsis	0 (0.0)	1 (0.4)
Pneumonia	0 (0.0)	1 (0.4)
Pyelonephritis	0 (0.0)	1 (0.4)
Postoperative wound infection	0 (0.0)	1 (0.4)
Sepsis	1 (0.4)	0 (0.0)
Sepsis due to salpingo-oophoritis	1 (0.4)	0 (0.0)
Septic shock	1 (0.4)	1 (0.4)
Urinary tract infection	0 (0.0)	2 (0.7)
Injury, poisoning and procedural complications	**1 (0.4)**	**0 (0.0)**
Infusion related reaction	1 (0.4)	0 (0.0)
Neoplasms benign, malignant ,unspecified	**2 (0.7)**	**1 (0.4)**
Colon cancer	1 (0.4)	1 (0.4)
Rectal neoplasm	1 (0.4)	0 (0.0)
Nervous system disorders	**0 (0.0)**	**2 (0.7)**
Cerebrovascular accident	0 (0.0)	1 (0.4)
Convulsion	0 (0.0)	1 (0.4)
Renal and urinary disorders	**2 (0.7)**	**0 (0.0)**
Azotemia	1 (0.4)	0 (0.0)
Calculus ureteric	1 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.4)**	**1 (0.4)**
Aspiration	1 (0.4) **	0 (0.0)

Pulmonary embolism	0 (0.0) **	1 (0.4)
Vascular disorders	**1 (0.4)**	**1 (0.4)**
Deep vein thrombosis	1 (0.4)	0 (0.0)
Thrombophlebitis superficial	0 (0.0)	1 (0.4)
Source: CSR, 505, Table-40 *Sudden cardiac death should have been categorized in cardiac Disorders. ** These SAEs resulted in death.		

The following table presents an overview of the system organ classes (SOCs) in which these SAEs occurred in the two treatment groups.

Table 73 Summary of serious adverse events (SAEs) by MedDRA System Organ Class (SOC) and PT in All Treated Pool, Safety Population.

SAEs, occurred in Overall Safety Pool of mer-vab development program by MedDRA SOCs and PT				
MedDRA SOC	**MedDRA PT**	**Mer-Vab N=407**	**Comparator N=338**	**Total**
Cardiac disorders	Cardiac failure congestive	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Cardiac arrest	1 (0.25%)	0 (0.00%)	1 (0.13%)
General d/o and administration site conditions	Sudden cardiac death	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Multiple organ dysfunction syndrome	1 (0.25%)	0 (0.00%)	1 (0.13%)
Gastrointestinal disorders	Diarrhea hemorrhagic	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Gastrointestinal hemorrhage	1 (0.25%)	0 (0.00%)	1 (0.13%)
Infections and infestations	Septic shock	2 (0.49%)	3 (0.89%)	5 (0.66%)
	Pneumonia	0 (0.00%)	1 (0.30%)	1 (0.13%)
	Salpingo-oophoritis	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Klebsiella bacteremia	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Sepsis	2 (0.49%)	3 (0.89%)	5 (0.66%)
	Pyelonephritis	0 (0.00%)	1 (0.30%)	1 (0.13%)
	Postoperative wound infection	0 (0.00%)	1 (0.30%)	1 (0.13%)
	Clostridium difficile colitis	0 (0.00%)	1 (0.30%)	1 (0.13%)
	Peritonitis	0 (0.00%)	1 (0.30%)	1 (0.13%)
	Urinary tract infection	0 (0.00%)	2 (0.59%)	2 (0.27%)
	Bacterial sepsis	0 (0.00%)	1 (0.30%)	1 (0.13%)
Injury, poisoning and procedural complications	Infusion related reaction	1 (0.25%)	0 (0.00%)	1 (0.13%)
Neoplasms benign, malignant and unspecified (e.g. cysts and polyps)	Prostate cancer metastatic	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Rectal neoplasm	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Colon cancer	1 (0.25%)	1 (0.30%)	2 (0.27%)
Nervous system disorders	Seizure	0 (0.00%)	2 (0.59%)	2 (0.27%)
	Lacunar stroke	0 (0.00%)	1 (0.30%)	1 (0.13%)

Renal and urinary disorders	Acute kidney injury	0 (0.00%)	1 (0.30%)	1 (0.13%)
	Ureterolithiasis	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Azotemia	1 (0.25%)	0 (0.00%)	1 (0.13%)
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1 (0.25%)	1 (0.30%)	2 (0.27%)
	Aspiration	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Pneumonia aspiration	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Pulmonary edema	1 (0.25%)	0 (0.00%)	1 (0.13%)
Vascular disorders	Thrombophlebitis superficial	0 (0.00%)	1 (0.30%)	1 (0.13%)
	Deep vein thrombosis	1 (0.25%)	0 (0.00%)	1 (0.13%)
	Shock hemorrhagic	1 (0.25%)	0 (0.00%)	1 (0.13%)
Source: Clinical Reviewers' Analysis				

Reviewers' Comment*: As seen in the table above, SAEs that occurred only in the mer-vab group were from Cardiac SOCs, and General disorders and administration site conditions. One patient with SAE of sudden cardiac death was included by the Applicant in category of 'General disorders and administration site conditions', however, it should be classified in SOC of Cardiac Disorders. When the specific PT's characterized as SAEs in these SOCs were examined, it was apparent that many were related to the underlying comorbid condition or the progression of the disease and the index infection, rather than to an adverse event per se of meropenem-vaborbactam.*

Overall, frequencies of serious adverse events were similar among the two groups. (5.4% and 5.3% in the mer-vab and comparator groups, respectively). However, frequency of events differed by MedDRA System Organ Classes. Serious adverse events related to cardiac disorder were more frequent in the mer-vab group (as mentioned above), whereas, SAEs related to infections and infestations accounted for the majority of the SAEs in the comparator group.

Table below displays the SAEs occurred in >1 patient in All Treated Pool of the mer-vab development program.

Table 74 SAEs (Occurred in >1 patients in Phase 3 and All Treated Pools, Safety Population.

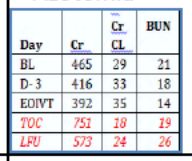
	Phase-3 Pool		***All Treated Pool***	
MedDRA Preferred Term	Mer-vab (N=295) n (%)	Comparators (N=289) n (%)	Mer-vab (N=407) n (%)	Comparator (N=338) n (%)
No. of Patients with any SAE	20 (6.8)	18 (6.2)	22 (5.4)	18 (5.3)
Sepsis	2 (0.7)	3 (1.0)	2 (0.5)	3 (0.9)
Septic shock	2 (0.7)	3 (1.0)	2 (0.5)	3 (0.9)
Colon cancer	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Pulmonary embolism	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Urinary tract infection	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)
Seizures	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)
Source: ISS, Table 21				

***Reviewers' Comment**: The most frequent SAEs (>1 patient overall), reported in both treatment groups included sepsis, septic shock, colon cancer, and pulmonary embolism. SAEs of urinary tract infection and seizures were reported for 2 subjects each in the comparator group.*

A brief Summary of all patients with SAEs in the mer-vab group (All Treated pool) and its association with study drug and outcome is presented in the Table below.

Table 75 Summary of SAEs occurred in the Meropenem-Vaborbactam Group in All Treated Pool, Safety Population

No.	Patient ID/Gender/ Age/Region/ Infection type	Cr CL group	DM/SIRS/ CCS	During Treatment Period (Y/N)	Study Drug Start Date/ End Date	AE Start day (Study Day)	AE End Day (Study Day)	SAE (s) [MedDRA Preferred Term]	Withdrawn from Study Drug /Study (YY/NN)	SAE Severity	Relation to Drug	Outcome
Study-506												
1	506-840-019-603 61/M/W/USA cUTI	>=30 - 50	Y/Y/ 15	Y	10/21-10/27	6	12	Multiple organ dysfunction syndrome	Y/Y	Severe	Unlikely related	Fatal
2 (2)	506-376-005-603/74/F/W/ Eur/ Bacteremia	>=30 - 50	Y/Y/ 9	N	2/3-2/6	4	5	1)-Shock Hemorrhagic; 2)- GI He	Y/Y	Severe	Not related	Fatal
3	506-300-001-610/ 88/F/W/Eur/ AP	<30	N/Y/ 5	N	2/23-2/25	3	4	Sepsis	N/ Y	Severe	Not related	Fatal
4	506-300-001-609/ 65/ F/W/ Eur/ AP	>50	Y/ N/ 7	N	2/2-2/9	17	35	Septic Shock	N /Y	Severe	Not related	Fatal
5	506-300-001-601/ 69/F/W/Eur/ Bacteremia	>=30 - 50	Y/N/ 5	N	9/4-9/7	4	4	Cardiac arrest	Y/Y	Severe	Not related	Fatal
6	506-300-001-613/	<30	N/N/	Y	3/9-	11	12	Pulmonary	N/N	Severe	Not	Recovered

No.	Patient ID/Gender/ Age/Region/ Infection type	Cr CL group	DM/SIRS/ CCS	During Treatment Period (Y/N)	Study Drug Start Date/ End Date	AE Start day (Study Day)	AE End Day (Study Day)	SAE (s) [MedDRA Preferred Term]	Withdrawn from Study Drug /Study (YY/NN)	SAE Severity	Relation to Drug	Outcome
(2)	83/M/W/Eur/ c-UTI		9		3/22			Edema [2 episodes]			related	
7	506-376-001-601/ 69/M/W/Eur/ Bacteremia	>50	N/N/ 9	N	1/25-2/8	20	25	Klebsiella Bacteremia (Recurrence)	N/N	Severe	Not related	Recovered
8	506-300-001-614/ 82/M/W/ Eur/ HABP	>50	N/Y/ 9	N	3/20-3/29	17	31	Pulmonary Aspiration		Severe	Not related	Recovered
9	506-300-001-602/ 78/F/W/Eur/ AP	>50	N/N/ 5	Y	10/29-11/10	6	13	Pulmonary Embolism	N/N	Moderate	Not related	Recovered
Study-505												
10	505-203-002-503/74/M/W/ Eur/ cUTI	>50	N/N/ 4	N	8/6- 8/15	11	11	Sudden Cardiac Death	N/ Y	Severe	Not related	Fatal
11	505-076-003-510/ 76/M/W/Rest of World/cUTI	>=30-50	N/N/ 7	N	3/14-3/22	13	14	Aspiration	N/ Y	Severe	Not related	Fatal
12	REMPEX-505-804-009-524/ 49/M/W/Eur/ cUTI	<30	N/N/ 3	N	2/11-2/21	14	22	Azotemia 	N/N	Severe	Not related	Recovered
13	REMPEX-505-804-007-501/ 44/M/W/Eur/ cUTI	>50	N/N/ 1	Y	6/4- 6/15	5	11	Ureterolithiasis	N/N	Moderate	Not related	Recovered

Day	Cr	Cr CL	BUN
BL	465	29	21
D-3	416	33	18
EOIVT	392	35	14
TOC	751	18	19
LFU	573	24	26

No.	Patient ID/Gender/ Age/Region/ Infection type	Cr CL group	DM/SIRS/ CCS	During Treatment Period (Y/N)	Study Drug Start Date/ End Date	AE Start day (Study Day)	AE End Day (Study Day)	SAE (s) [MedDRA Preferred Term]	Withdrawn from Study Drug /Study (YY/NN)	SAE Severity	Relation to Drug	Outcome
14	REMPEX-505-804-003-505/ 38/F/W/Eur/AP	>=30 - 50	N/Y/ 0	N	7/11-7/20	15	30	Deep Vein Thrombosis	N/N	Moderate	Not related	Recovered
15	505-705-002-502/ 71/M/W/Eur/ cUTI	>50	N/Y/ 5	Y	8/29-8/31	2	2	Cardiac Failure Congestive	N/N	Severe	Not related	Recovered
16 [2]	505-703-005-510/ 42/F/W/Eur cUTI	>50	N/N/ 1	Y	10/29-10/30	2	6	Septic Shock	Y/Y	Severe	Not related	Recovered
						2	13	Salpingo-oophoritis				
17	505-642-003-503/ 69/M/W/Europe/ cUTI	>50	N/N/ 3	Y	12/4-12/9	6	Not given	Rectal Neoplasm	N/N	Mild	Not related	Unknown
18	505-616-003-507/ 70/F/W/Eur/AP	>50	Y/N/ 8	Y	11/16-11/26	9	N/A	Colon Cancer	N/N	Severe	Not related	Unknown
19	505-604-004-502/ 67/M/Other/ Rest of World/AP	>50	N/N/ 3	Y	11/5-11/5	1	1	Infusion related reaction	Y/ N	Severe	Probably related	Recovered
20	505-076-003-506/ 73/M/W/Rest of World/ cUTI	>50	N/N/ 5	N	10/15-10/24	18	33	Sepsis	N/N	Moderate	Not related	Resolved
Study- 504*												
21	504-05-637/ 43/M/W/USA/ Gr-5 ESRD	<30	N/N/ 0	N	7/25-7/25	6	Not given	Prostate Cancer (metastatic)	Y/ N	Severe	Not related	NOT Resolved
22	504-05-634/ 69/M/Black/USA/ Gr-5 ESRD	<30	N/N/0	N	7/12-7/19	9	10	Diarrhea Hemorrhagic	N/N	Severe	Possibly Related	Resolved

No.	Patient ID/Gender/ Age/Region/ Infection type	Cr CL group	DM/SIRS/ CCS	During Treatment Period (Y/N)	Study Drug Start Date/ End Date	AE Start day (Study Day)	AE End Day (Study Day)	SAE (s) [MedDRA Preferred Term]	Withdrawn from Study Drug /Study (YY/NN)	SAE Severity	Relation to Drug	Outcome
Source: Clinical Reviewers' Analysis, ISS, Multiple sources *Subjects received Two doses of 1 g meropenem + 1 g vaborbactam IV infused over 3 hr. CCS=Charlson Comorbidity Score; Hge=Hemorrhage; GI= gastrointestinal; M= male; F= female; W= white; N= No; Y= yes; CrCL= creatinine clearance in ml/min; ESRD= end stage renal disease; N/A= Not available												

***Reviewers' Comment**: There were 11 SAEs in Study 505, 9 SAEs in Study 506, and 2 SAEs in Phase 1 trial, Study 504 in the mer-vab group. SAEs that were considered by the Investigator as related to study drug were one event of 'infusion related hypersensitivity reaction in Study 505 and an event of 'hemorrhagic diarrhea' in Study 504. Fatal SAEs were discussed in section 8.4.1. A brief narrative of the SAEs which were considered by the Investigator as possibly or probably related to study drug are presented below.*

Case # 604-004-502 (SAE of infusion related hypersensitivity reaction)

This was a 67- year-old male of mixed race with a history of prostatectomy, who was enrolled in Study 505 with the diagnosis of acute pyelonephritis (AP). He was also hypertensive at the time of enrollment. On study day 1 patient was reported to be in a good general state and with stable vital signs. During the study drug infusion, at 19:55, the patient became hypotensive with a blood pressure (BP) of 70/40 mmHg. At 19:57, an electrocardiogram revealed atrial fibrillation with rapid ventricular response (ventricular heart rate of 187 bpm) and marked left precordial repolarization disturbance. Initial treatment included IV normal saline bolus. The patient's condition showed no improvement and the patient was hemodynamically unstable. Study drug infusion was held at 20:03. The site logged into the IWRS and conducted an emergency unblinding. Additional treatment included IV lanatoside, polygeline, midazolam, fentanyl, and warfarin. At 21:00, the subject was intubated and underwent successful electrical cardioversion, converting to sinus rhythm after the first attempt (100 joules). The patient was closely monitored and remained hemodynamically stable. At 22:30, the subject was extubated. He awoke and was able to sustain spontaneous breathing; cardiac monitoring revealed sinus rhythm at 89 bpm; amikacin was initiated; and the event of infusion related reaction was considered resolved. The study drug was discontinued due to the event. The patient continued in the study.

Case # 504-05-634 (Hemorrhagic Diarrhea)

This was a 68-year-old African American male with End Stage Renal Disease (ESRD) who was hospitalized due to bloody diarrhea while participating in Study 504. On (b) (6) the subject initiated study therapy with meropenem-vaborbactam 1 g/1 g via intravenous infusion over 3 hours during Period 1 of the study. The dosing was uneventful, and he was released next day. He was re-admitted to the clinical research in 5 days on (b) (6), for Period 2 of the study and reported no changes in health or medications. He received his Period 2 dosing on (b) (6) at 11:45 following a regularly scheduled hemodialysis therapy. Dosing was uneventful. On (b) (6), the subject reported mild abdominal discomfort. Because he had a history of GERD, he was given calcium carbonate antacid. At approximately 16:00, he began having diarrhea that became bloody. He had about six stools with volume of approximately 800 mL. He was sent to the Emergency Department for evaluation of "lower GI bleeding". Upon admission, hemoglobin was 6.9 g/dL (normal: 13.1-17.5 g/dL), hematocrit was 21.6% (normal range: 40.0%-51.0%), RBC count was 2.77 million/mm^3 (normal range: 4.60-6.00 million/mm^3), and platelets were 179 thousand/mm^3 (normal range: 150-400 thousand/mm^3). Two units of packed RBCs were transfused, and the post-transfusion hemoglobin was 7.8 g/dL. Bedside echocardiogram and ultrasound of the abdomen demonstrated normal findings. Later that evening ((b) (6)), he was transferred to the medical intensive care unit (MICU) for closer evaluation. On (b) (6), subject underwent a colonoscopy and endoscopy. Colonoscopy displayed multiple small and large-mouthed diverticuli in the sigmoid and ascending colon. No blood or the source of bleeding was identified; the attending physician suggested that the

diverticuli could have been a source of bleeding. Upper gastrointestinal endoscopy demonstrated normal esophagus, stomach, and duodenum with no blood or source of bleeding identified. Results of C*. difficile* toxin testing were not available. The SAE was considered recovered/resolved on the day of colonoscopy and the patient was discharged from the hospital with stable hemoglobin and vital signs on (b) (6). The Investigator assessed subject's bloody diarrhea as National Cancer Institute Common Toxicity Criteria (NCI CTC) AE grade 3/severe and possibly related to study drug. The abdominal pain was considered by investigator as unlikely related to study drug. There were no additional SAEs concurrent with this event.

Prior to the event, the subject was also taking the following concomitant medications: calcium acetate, One-A-Day Men's Multivitamin, Odorless Garlic, amlodipine besylate, acetaminophen, furosemide, aspirin, etoprolol, Sensipar, Losartan potassium, and pantoprazole sodium. The subject had a complex medical history including chronic kidney disease (since 2002), ESRD (since 2012), AV fistula (since 2012), diabetes type 2 (since 2004) and alcohol use (1969-2012).

Reviewers' Comment*: In this reviewers' opinion, the study drug was not the cause of this SAE of bloody diarrhea. The subject was found to have extensive multiple diverticuli, and that was probably the cause of this subjects' bleeding. Diverticular bleeding is known to start suddenly and usually stops on its own.*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The Figure below displays the overview of premature treatment discontinuation in Safety Population (All Treated Pool).

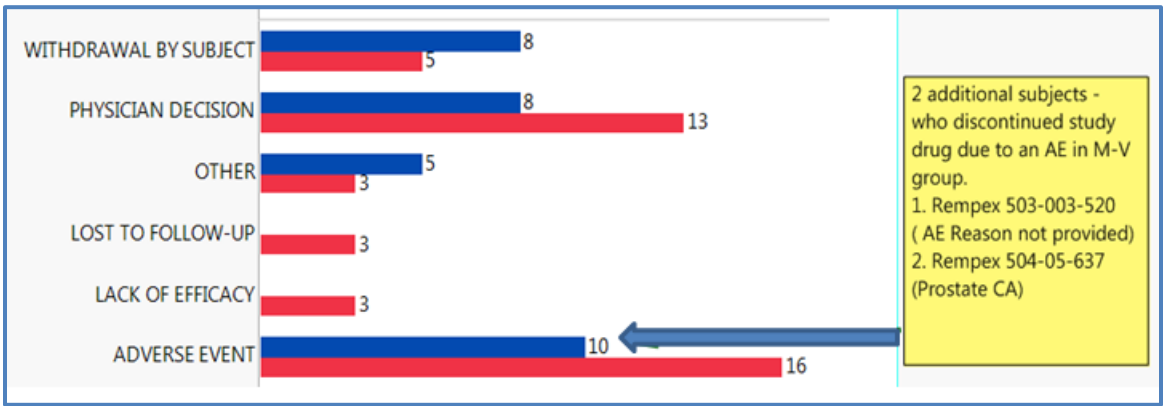


Figure 6 Premature treatment discontinuation in Safety Population (All Treated Pool)

Reviewers' Comment*: Patient disposition was discussed in detail in section 6.1.3, and 6.2.2. In this section, adverse events leading to study drug discontinuation are examined. There was a minor discrepancy between this reviewer's analysis and that of the Applicant. For example, in "adverse events" category, there were 2 patients in the mer-vab group in Phase 1 trials who discontinued treatment due to an adverse event. The Applicant did not include these patients in the disposition table; however, this reviewer felt that because study drug was discontinued due to an AE, and one AE was possibly related to the infusion, these subjects should be included.*

One subject from Study 503(# 503-003-520), who was 25- year-old Black male, developed moderate AE of chest pain and discomfort along with lightheadedness and dyspnea. Symptoms resolved after discontinuation of the study drug. This subject was withdrawn from study as well.

Another subject (# 504-05-637) from renal impairment study, a 43yearold white male enrolled in the ESRD cohort was diagnosed with metastatic prostate cancer, which was not related to study drug. However, the study drug was withdrawn since AE was considered severe leading to hospitalization of the patient.

Table below displays adverse events leading to study drug discontinuation in >1 subjects in the Phase 3 Pool and All Treated Pool.

Table 76 AEs Leading to Discontinuation of Study Drug in>1 Subject Overall (Safety Population)

	Phase 3 Pool		**All Treated Pool**	
Preferred Term	**Mer-vab N=295 n (%)**	**Comparator N=289 n (%)**	**Mer-vab N=407 n (%)**	**Comparator N=338 n (%)**
# of Subjects with any AE leading to discontinuation of study drug	10 (3.4)	16 (5.5)	12* (2.9)	16 (4.7)
Pyrexia	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Drug hypersensitivity	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Hypersensitivity	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Septic shock	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Infusion related reaction	2 (0.7)	0 (0.0)	2 (0.5)	0 (0.0)

Source: ISS, Table 22
*2 subjects from Phase 1 trials, which were discussed above.

Reviewers' Comment*: In the Phase-3 Pool, other than an 'infusion-related reaction' which led to study drug discontinuation in 2 (0.7%) patients in the mer-vab group and 0 patients in the comparator group; and 'hypersensitivity' leading to discontinuations in 2 (0.7%) patients in each*

group. All other AEs leading to study drug discontinuation occurred in no more than 1 patient in either treatment group.

The most frequently reported (>1 subject overall) AEs leading to study drug discontinuation were pyrexia, drug hypersensitivity, hypersensitivity, septic shock, and infusion related reaction (one of the two infusion-related reactions was also an SAE). Similar results were noted in the All Treated Pool.

8.4.4. Significant Adverse Events

In the Phase 3 Pool, the distribution of TEAE severity was as follows:

Table 77 Severity of TEAEs in the Phase 3 Pool, Safety Population

	Phase 3 Pool			
	Mer-vab N=295		Comparator N=289	
	# Of Patients (n %)	# Events	# Of Patients (n %)	# Events
All TEAEs	126 (42.7)	269	111 (38.4)	244
Drug-Related TEAEs	47 (15.9)	67	44 (15.2)	63
TEAE by Maximum Severity				
All TEAEs	126 (42.7)	188	111 (38.4)	165
Mild	54 (18.3)	86	48 (16.6)	80
Moderate	48 (16.3)	74	39 (13.5)	54
Severe	12 (4.1)	15	19 (6.6)	26
Life threatening	5 (1.7)	6	0 (0.0)	0
Death	7 (2.4)	7	5 (1.7)	5
Drug Related TEAEs	47 (15.9)	60	44 (15.2)	54
Mild	26 (8.8)	32	22 (7.6)	25
Moderate	18 (6.1)	25	18 (6.2)	23
Severe	2 (0.7)	2	3 (1.0)	5
Life threatening	1 (0.3)	1	1 (0.3)	1
Death	0	0	0	0
TEAE leading to Deaths	7 (2.4)	7	5 (1.7)	5
Source: ISS and , Clinical Reviewers' Analysis				

***Reviewers' Comment**: Comparatively more patients in the mer-vab group developed TEAEs of mild and moderate intensity, whereas severe TEAEs were higher in the comparator group. However, life-threatening TEAEs were only seen in the mer-vab group. These life-threatening events included: congestive cardiac failure, septic shock secondary to salpingo-oophoritis, infusion-related hypersensitivity reaction, aspiration pneumonia, and pulmonary edema. All of these events were nonfatal, but serious AEs. The infusion-related reaction (Patient # 505-604-*

004-502) was the only one of these life-threatening events that was considered related to study drug. This event led to study drug discontinuation. The remaining four events were attributed to the patients' underlying comorbidities or progression of illness and infections.

Severe TEAEs occurred in 12 (4.1%) of patients in the mer-vab group and 19 (6.6%) of patients in the comparator group. These accounted for 15/188 events and 26/165 events, in the mer-vab and comparator groups, respectively. Severe TEAEs reported for more than 1 patient included anemia (3 [1.0%] patients in each treatment group), seizure (0 patients in the mer-vab group and 2 [0.7%] patients in the comparator group), aspartate aminotransferase increased (1 [0.3%] in each treatment group), and colon cancer (1 [0.3%] in each treatment group).

The SAEs are discussed in Section 8.4.2. Severe TEAEs that were not characterized as SAEs are displayed in the table below.

Table 78 Severe TEAEs that were not characterized as SAEs (Phase-3 Pool)

			Treatment Group	
AE by SOC	**AE by PT**	**Study-ID**	**M-V**	**COMP**
Blood and lymphatic disorders	Anemia	505	1	2
Blood and lymphatic disorders	Anemia	506	2	2
Hepatobiliary disorders	Bile duct stone	505	1	0
Infections and infestations	Bacteremia	506	0	1
Infections and infestations	Pseudomonal bacteremia	506	0	1
Injury, poisoning and procedural	Infusion related reaction	505	1	0
Investigations	ALT increased	505	0	1
Investigations	AST Increased	505	1	1
Investigations	Blood CPK increased	505	0	1
Investigations	Blood creatinine increased	505	0	1
Investigations	Fibrin D dimer increased	505	0	1
Investigations	Blood ALP increased	506	1	0
Metabolism and nutrition disorders	Hypoglycemia	505	1	0
Metabolism and nutrition disorders	Hypokalemia	505	1	0
Psychiatric disorders	Confusional state	506	0	1
Renal and urinary disorders	Oliguria	505	1	0
Renal and urinary disorders	Ureteric obstruction	505	1	0
Renal and urinary disorders	Acute kidney injury	506	0	1
Renal and urinary disorders	Renal impairment	506	0	1
Respiratory, thoracic disorders	Dyspnea	505	0	1
Respiratory, thoracic disorders	Pneumonia aspiration	505	0	1
Respiratory, thoracic disorders	Hypoxia	506	1	0

Respiratory, thoracic disorders	Pneumothorax	506	0	1
Respiratory, thoracic disorders	Pulmonary embolism	506	1	0
Vascular disorders	Hypertension	505	1	0
M-V: meropenem-vaborbactam; COMP: comparator Source: Clinical Reviewers' Analysis				

Reviewers' Comment*: In Phase 1 trials, Severe TEAEs which were not considered serious were infusion site phlebitis in Study 501 (3 events in 2 subjects). TEAES which were severe and serious occurred in 2 patients in Renal Impairment Study 504 (Both patients were in Group-5, ESRD). Patient # 504-05-634 had hemorrhagic diarrhea which was considered possibly related to study drug, and patient # 504-05-637 had a diagnosis of metastatic prostate cancer, not related to study drug.*

Laboratory abnormalities characterized as severe included: alanine aminotransferase increase (1 in comparator), aspartate amino transferase increased (1 in each treatment group), blood creatine phosphokinase increased (1 in comparator), blood creatinine increased (1 in comparator), hypoglycemia and hypokalemia (1 each in the mer-vab group), and fibrin-D dimer increased (1 in the comparator group). As can be seen, many of the severe TEAEs were related to underlying disease or its complications.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

While examining TEAEs in the pivotal trial for cUTI (Study 505), the proportion of patients who experienced one or more TEAE was 106 (39.0%) in the mer-vab group and 97 (35.5%) in the pip-tazo group. The proportion of patients who had TEAEs in the mer-vab and pip-tazo groups that were related to study drug (15.1% and 12.8%, respectively), severe AE (2.6% and 4.8%, respectively), SAE (4% and 4.4%, respectively), AE leading to study drug discontinuation (2.6% and 5.1%, respectively) or discontinuation from study (1.1% in each group) was also similar. However, as mentioned earlier, life threatening TEAEs were a little higher in the mer-vab group (3 patients in the mer-vab group as compared to zero patients in the pip-tazo group). Mortality was similar in both groups. Two patients (0.7%) in each group died in Study-505 (Table below). All deaths in Study 505 were assessed as unrelated to study drug.

Table 79 Treatment Emergent Adverse Events (TEAE) - Study 505 (Safety Population)

	Mer-vab (N=272)		**Pip-tazo (N=273)**	
	Patients, n (%)	**Events (n)**	**Patients, n (%)**	**Events (n)**
All TEAEs	106 (39.0)	204	97 (35.5)	170
Drug-related TEAEs^	41 (15.1)	56	35 (12.8)	45
TEAEs by Severity				

	Mer-vab (N=272)		Pip-tazo (N=273)	
	Patients, n (%)	**Events (n)**	**Patients, n (%)**	**Events (n)**
Mild	49 (18.0)	79	45 (16.5)	69
Moderate	45 (16.5)	71	37 (13.6)	48
Severe	7 (2.6)	9	13 (4.8)	15
Life-Threatening	3 (1.1)	3	0 (0.0)	0
All SAEs	11 (4.0)	12	12 (4.4)	12
Drug-related SAEs	1 (0.4)	1	1 (0.4)	1
Deaths	2 (0.7)	2	2 (0.7)	2
Discontinuation of study drug due to TEAEs*	7 (2.6)	8	14 (5.1)	16
Discontinuation from study due to TEAEs**	3 (1.1)	4	3 (1.1)	4

Source: Clinical Reviewers' Analysis and Applicant's Table 36

* Includes 2 subjects with fatal AEs in the pip-tazo group.
** Includes 2 subjects in the mer-vab group with fatal AEs and 1 subject in the pip-tazo group with a fatal AE.
^ Drug-related TEAEs includes TEAEs that were possibly and probably related to study drugs.
Note: TEAEs are AEs with a start date and time on or after the first dose of study drug.

Similar trend was observed among 745 patients that make up the overall safety population. As shown in the table, the proportions of all TEAEs, and drug related TEAEs; mild, moderate and severe TEAEs were similar in overall safety population. However, as seen in Study-505, life-threatening TEAEs were comparatively higher in the mer-vab group. Adverse events leading to study drug discontinuation are already discussed in section 8.4.3 of this review.

Table 80 Treatment Emergent Adverse Events (Phase 3 Pool and All Treated Pool, Safety Population)

	Phase 3 Pool		All Treated Pool	
	Mer-vab N=295 n (%)	**Comparator N=289 n (%)**	**Mer-vab N=407 n (%)**	**Comparator N=338 n (%)**
All TEAEs	126 (42.7)	111 (38.4)	184 (45.2)	156 (46.2)
Drug-related TEAEs	47 (15.9)	44 (15.2)	88 (21.6)	74 (21.9)
TEAE by Maximum Severity	126 (42.7)	111 (38.4)	184 (45.2)	156 (46.2)
Mild	54 (18.3)	48 (16.6)	94 (23.1)	83 (24.6)
Moderate	48 (16.3)	39 (13.5)	62 (15.2)	49 (14.5)
Severe	12 (4.1)	19 (6.6)	16 (3.9)	19 (5.6)
Life-Threatening	5 (1.7)	0 (0.0)	5 (1.2)	0 (0.0)
All SAEs	20 (6.8)	18 (6.2)	22 (5.4)	18 (5.3)
Drug-related SAE	1 (0.3)	3 (1.0)	2 (0.5)	3 (0.9)
Deaths	7 (2.4)	5 (1.7)	7 (1.7)	5 (1.5)
Discontinuation of study drug Due to TEAEs	10 (3.4)	16 (5.5)	12 (2.9)	16 (4.7)
Discontinuation from study due to TEAEs**	8 (2.7)	6 (2.1)	9 (2.2)	6 (1.8)
Source: Applicant's Table 14, ISS				

***Reviewers' Comment**: In general, there does not seem to be a significant imbalance in the frequency of adverse events for the mer-vab group compared to the comparator group besides frequency of life-threatening TEAEs which were higher in the mer-vab group. Life-threatening AEs which were found in the mer-vab group only (3 patients in Study-505) included congestive cardiac failure in Subject 705-002-502, septic shock secondary to salpingo-oophoritis in Subject 703-005-510, and an infusion-related reaction in Subject 604-004-502. All 3 of these events were nonfatal, serious AEs. The infusion-related reaction was the only one of these events considered related to study drug by the investigator.*

All deaths occurred in Phase-3 trials and the incidence of AEs was balanced between treatment groups.

Table below summarizes the reported TEAEs by MedDRA SOC classification for Phase 3 and All Treated Pools.

Table 81 Treatment Emergent Adverse Events by System Organ Class in Phase 3 and All treated Pools (Safety Population)

	Phase-3 Pool		All Treated Pool	
	M-V (N=295) n (%)	Comparators (N=289) n (%)	M-V (N=407) n (%)	Comparators (N=338) n (%)
Total subjects with TEAEs	126 (42.7)	111 (38.4)	184 (45.2)	156 (46.2)
MedDRA SOC				
General disorders and administration site	31 **(10.5)**	13 (4.5)	68 (16.7)	50 (14.8)
Nervous system disorders	30 **(10.2)**	19 (6.6)	54 (13.3)	38 (11.2)
Gastrointestinal disorders	27 (9.2)	33 (11.4)	50 (12.3)	42 (12.4)
Infections and infestations	26 (8.8)	37 **(12.8)**	29 (7.1)	40 (11.8)
Respiratory, thoracic and mediastinal	15 (5.1)	15 (5.2)	17 (4.2)	17 (5.0)
Investigations	13 (4.4)	15 (5.2)	14 (3.4)	15 (4.4)
Metabolism and nutrition disorders	11 (3.7)	10 (3.5)	12 (2.9)	12 (3.6)
Vascular disorders	11 (3.7)	8 (2.8)	11 (2.7)	9 (2.7)
Skin and subcutaneous tissue disorders	6 (2.0)	8 (2.8)	12 (2.9)	14 (4.1)
Renal and urinary disorders	9 (3.1)	10 (3.5)	10 (2.5)	10 (3.0)
Cardiac disorders	8 (2.7)	8 (2.8)	8 (2.0)	9 (2.7)
Blood and lymphatic system disorders	6 (2.0)	9 (3.1)	6 (1.5)	9 (2.7)
Musculoskeletal and connective tissue	8 (2.7)	1 (0.3)	14 (3.4)	4 (1.2)
Injury, poisoning and procedural	6 (2.0)	3 (1.0)	10 (2.5)	5 (1.5)
Psychiatric disorders	3 (1.0)	4 (1.4)	5 (1.2)	4 (1.2)
Eye disorders	3 (1.0)	1 (0.3)	5 (1.2)	3 (0.9)

	Phase-3 Pool		All Treated Pool	
	M-V (N=295) n (%)	Comparators (N=289) n (%)	M-V (N=407) n (%)	Comparators (N=338) n (%)
Immune system disorders	3 (1.0)	2 (0.7)	4 (1.0)	2 (0.6)
Hepatobiliary disorders	3 (1.0)	1 (0.3)	3 (0.7)	1 (0.3)
Neoplasms benign, malignant and unspecified	2 (0.7)	1 (0.3)	3 (0.7)	1 (0.3)
Reproductive system and breast disorders	1 (0.3)	1 (0.3)	2 (0.5)	3 (0.9)
Endocrine disorders	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Ear and labyrinth disorders	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Product issues	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Source: Clinical reviewers' Analysis M-V= meropenem-vaborbactam				

The most frequent TEAEs in the Phase 3 Pool and overall safety population were observed in the SOCs of general disorders and administration site conditions, nervous system disorders, gastrointestinal disorders and infections and infestations. Among these, apart from infections and infestations, the incidence of TEAEs in these SOCs was comparatively higher in the mer-vab group. The most frequent TEAEs in the Phase 3 Pool by preferred terms were headache, diarrhea, infusion-site phlebitis, and nausea. These were balanced between the two groups except for headaches. Headache occurred at a ≥2% higher incidence in the mer-vab group than in the comparators group. No 'severe' headaches were reported and none of the headaches in either group were 'serious' or resulted in discontinuation of study drug or discontinuation from the study.

Similar results were seen in the All Treated Pool. The most frequent TEAEs in this pool included headache, infusion-site phlebitis, diarrhea, infusion site pain, and nausea. Headache was the only TEAE that occurred at a ≥2% higher incidence in the mer-vab group than in the comparator group.

TEAEs of infusion site pain were reported for 4.4% of subjects in the mer-vab group and 2.7% of subjects in the comparator group, and all were reported in Phase 1 Study 501 in healthy volunteers.

TEAEs by SOCs that were disproportionately higher in the mer-vab group (General disorders and administration site conditions, and Nervous system disorders) are summarized in subsequent tables below by Preferred Terms.

Table 82 TEAEs from SOC - General Disorders and Administration Site Conditions (GDAS) in All Treated Pool, Safety Population

		Treatment Groups	
MedDRA PT	**Relatedness**	**Mer-vab**	**Comparators**
Application site erythema	Not Related	1	1
Application site pruritus	Not Related	0	1
Asthenia	Not Related	1	1
	Related	**0**	**1**
Calcinosis	Not Related	1	0
Catheter site bruise	Not Related	5	4
Catheter site erythema	Not Related	5	2
Catheter site hematoma	Not Related	1	0
Catheter site inflammation	Not Related	1	1
	Related	**1**	**0**
Catheter site pain	Not Related	7	4
Catheter site phlebitis	Not Related	8	5
	Related	**1**	**1**
Catheter site related reaction	Not Related	2	1
Chest discomfort	**Related**	**2**	**0**
Chest pain	Not Related	1	0
Chills	Not Related	1	0
	Related	**1**	**0**
Fatigue	Not Related	1	2
Feeling cold	Not Related	0	1
Generalized edema	Not Related	0	2
Infusion site bruising	Not Related	2	3
	Related	**3**	**1**
Infusion site discomfort	**Related**	**0**	**1**
Infusion site erythema	Not Related	1	1
	Related	**4**	**8**
Infusion site extravasation	Not Related	3	1
	Related	**2**	**1**
Infusion site fibrosis	Not Related	0	1
Infusion site pain	Not Related	4	2
	Related	**14**	**7**
Infusion site phlebitis	Not Related	1	0
	Related	**23**	**16**
Infusion site swelling	Not Related	0	1
	Related	**3**	**4**
Infusion site thrombosis	Not Related	1	0
Injection site phlebitis	Not Related	1	0
	Related	**1**	**0**
Malaise	Not Related	0	1
Multiple organ dysfunction syndrome *	Not Related	1	0
Edema peripheral	Not Related	0	1

		Treatment Groups	
MedDRA PT	**Relatedness**	**Mer-vab**	**Comparators**
	Related	**0**	**1**
Pain	Not Related	1	0
	Related	**0**	**1**
Peripheral swelling	Not Related	1	0
Pyrexia	Not Related	3	2
	Related	**3**	**1**
Sudden cardiac death *	Not Related	1	0
Vessel puncture site bruise	Not Related	7	3
Vessel puncture site erythema	Not Related	0	1
Vessel puncture site hematoma	Not Related	0	1
Vessel puncture site pain	Not Related	3	2
Vessel puncture site swelling	Not Related	0	1
Source: Clinical Reviewer' Analysis; Note: Only one instance of similar events in each subjects are noted here *Fatal events			

***Reviewers' Comment**: There was one TEAE, in the mer-vab group, which should have been classified in the category of Cardiac disorders, however, misclassified by the applicant in SOC of General disorder and administration site conditions as was mentioned earlier. This included a patient with a TEAE of 'sudden cardiac death' which was severe and fatal and should have been classified under SOC of cardiac disorders. This was a 71–year-old white, quadriplegic male in study 505 (505-203-002 503), enrolled from an European study site, who was enrolled with c-UTI. The patient was non-diabetic, no SIRS on presentation, with baseline creatinine clearance of 179, and a CCS score of 4. He received 10 days of study drug and was improving gradually. On study day 11, patient had a sudden loss of consciousness secondary to circulatory and respiratory arrest. Possible causes of the event were unknown. The event was deemed unrelated to study drug.*

TEAE of multiorgan failure (which was also severe and resulted in death) occurred in a 61-year-old white male patient with critical illness, in study-506 (REMPEX-506-840-019-603) with diagnosis of c-UTI, from North America with baseline creatinine clearance of 38, diabetic, CCI score of 15 and presented with SIRS. Multiorgan failure gradually developed on study day 6. Study drug was withdrawn and patient was started on other supportive and therapeutic measures. The patient eventually died on study day 12.

Table 83 TEAEs from SOC 'Nervous System Disorders' (All Treated Pool, Safety Population)

TEAEs from SOC 'Nervous System Disorders' (All Treated Pool)		
	All Treated Pool	
	Mer-vab N=407	**Comparator N=338**
	N (%)	N (%)
Cerebral arteriosclerosis	1 (0.25%)	0 (0.00%)
Dizziness	6 (1.47%)	6 (1.78%)
Encephalopathy	0 (0.00%)	1 (0.30%)
Headache	42 (10.32%)	25 (7.40%)
Hypoesthesia	0 (0.00%)	1 (0.30%)
Lacunar stroke	0 (0.00%)	1 (0.30%)
Lethargy	1 (0.25%)	0 (0.00%)
Migraine	0 (0.00%)	1 (0.30%)
Paranesthesia	5 (1.23%)	2 (0.59%)
Parousia	0 (0.00%)	1 (0.30%)
Presyncope	1 (0.25%)	1 (0.30%)
Seizure	0 (0.00%)	2 (0.59%)
Somnolence	0 (0.00%)	1 (0.30%)
Syncope	1 (0.25%)	0 (0.00%)
Tremor	2 (0.49%)	1 (0.30%)
Source: Clinical reviewers' Analysis		

***Reviewers' Comment**: Two cases of TEAE of tremor were reported in the mer-vab group. One in a patient in Study 505 as 'generalized body tremor', during study drug infusion on day 4; which was moderate, considered related to study drug and led to discontinuation of study drug. Another case of tremor reported in Study 506 as hand tremor which occurred on day 10, after the study drug was discontinued. It was mild and not considered related to study drug.*

Majority of other TEAEs from nervous system disorders were reported in Phase 1 trials.

There was 1 TEAE of syncope and 1 of presyncope, each was reported in Phase 1 trial (Study 501) on study day 5 and 7. Both were mild, categorized as vasovagal syncope and were not considered related to study drug.

There were 5 cases of paresthesia in the mer-vab group, 4 of those reported in Phase 1 trials (3 in Study 501, and 1 case in Study 504) and 1 case of paresthesia reported in Study 505.

Of 7 patients with TEAE of dizziness, 4 were reported in subjects in Phase 1 trial (Study 504), 1 patient in Study 503, and one patient in Phase-3 trial (Study 505).

Potential for neuro-motor impairment is addressed in the meropenem label to alert patients receiving meropenem in the outpatient setting about adverse events such as seizures, delirium, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment.

TEAEs from SOC Cardiac Disorders

The occurrence of TEAEs by preferred term (PT) in the SOC of Cardiac Disorders is tabulated below by subject IDs.

Table 84 TEAEs by Preferred Term (PT) in the Cardiac Disorders SOC (All Treated Poo, Safety Population)

		All Treated Pool	
Subject-ID	MedDRA PT	Mer-vab N=407	Comparators N=338
501- 02-02493	Palpitations	0	1
505-076-002-502	Bradycardia	0	1
505-100-006-504	Angina pectoris	0	1
505-100-007-508	Hypertensive heart disease	1	0
505-112-007-507	Arteriosclerosis coronary artery	1	0
505-642-001-513	Atrial fibrillation	0	1
505-642-001-514	Bundle branch block left	1	0
505-642-001-517	Bundle branch block right	1	0
505-642-002-505	Tachycardia	0	1
505-703-005-506	Palpitations	0	1
505-705-002-502	Cardiac failure congestive*	1	0
505-804-006-508	Angina pectoris	0	1
505-804-009-528	Myocardial ischemia	1	0
506-076-003-601	Atrial fibrillation	0	1
506-300-001-601	Cardiac arrest**	1	0
506-376-003-601	Atrial fibrillation	1	0
506-380-005-601	Extra systoles	0	2
506-826-001-601	Extra systoles	1	0
Source: Clinical Reviewers' Analysis *SAE; ** Fatal			

***Reviewers' Comment**: Systemic adverse events related to cardiac disorders were not seen in greater than 1% of patients with meropenem or other carbapenem class antibacterials.*

When specific PTs were examined as displayed in the table above, no specific signal was noted with mer-vab treatment. None of the PTs associated with cardiac disorders were considered

serious except 'congestive heart failure' in patient # 505-705-002-502, and 'cardiac arrest' in patient # 506-300-001-601. AE of cardiac arrest was fatal. Both of these AEs occurred in mer-vab group. The events were considered unrelated to study drug.

AEs which were assessed as possibly related were – 'palpitation' in subject #501-02-02493 from Phase-1 trial (Study 501); 'angina pectoris' in patient # 505-100-006-504 from Study 505; and extrasystole in patient # 506-380-005-601 from Study 506. All of these AEs occurred in the comparator group. None of these AEs caused discontinuation of study drug in the comparator group.

TEAEs by SOCs that occurred in >1% of subjects in the Phase 3 and All Treated Pools in either treatment group are presented in the table below.

Table 85 TEAEs That Occurred in >1% of Subjects in Either Treatment Group by Preferred Terms (Phase 3 and All Treated Pools)

	Phase-3 Pool		All Treated Pool	
	M-V (N=295)	Comparator (N=289)	M-V (N=407)	Comparator (N=338)
	n (%)	n (%)	n (%)	n (%)
Total subjects with TEAEs	**126 (42.7)**	**111 (38.4)**	**184 (45.2)**	**156 (46.2)**
MedDRA Preferred Terms				
Headache	26 (8.8)	12 (4.2)	42 (10.3)	25 (7.4)
Diarrhea	12 (4.1)	15 (5.2)	18 (4.4)	17 (5.0)
Infusion site phlebitis	7 (2.4)	2 (0.7)	24 (5.9)	16 (4.7)
Infusion site erythema	1 (0.3)	0 (0.0)	5 (1.2)	4 (1.2)
Injection site phlebitis	2 (0.7)	0 (0.0	2 (0.5)	0 (0.0)
Infusion site thrombosis	1 (0.3)	0 (0.0)	1 (0.0)	0 (0.0)
Nausea	6 (2.0)	5 (1.7)	14 (3.4)	8 (2.4)
Catheter site phlebitis	5 (1.7)	3 (1.0)	9 (2.2)	6 (1.8)
Alanine aminotransferase increased*	5 (1.7)	1 (0.3)	6 (1.5)	1 (0.3)
Aspartate aminotransferase increased*	4 (1.4)	2 (0.7)	4 (1.0)	2 (0.6)
Hypokalemia	4 (1.4)	6 (2.1)	4 (1.0)	6 (1.8)
Anemia	4 (1.4)	5 (1.7)	4 (1.0)	5 (1.5)
Asymptomatic bacteriuria	4 (1.4)	4 (1.4)	4 (1.0)	4 (1.2)
Urinary tract infection	4 (1.4)	4 (1.4)	4 (1.0)	4 (1.2)
Pyrexia	4 (1.4)	2 (0.7)	6 (1.5)	3 (0.9)
Vomiting	4 (1.4)	2 (0.7)	6 (1.5)	2 (0.6)
Constipation	3 (1.0)	4 (1.4)	5 (1.2)	6 (1.8)
Abdominal distension	3 (1.0)	2 (0.7)	5 (1.2)	2 (0.6)
Vulvovaginal candidiasis	2 (0.7)	5 (1.7)	2 (0.5)	5 (1.5)
Catheter site erythema	2 (0.7)	0 (0.0)	5 (1.2)	2 (0.6)

Considered Infusion related reactions

	Phase-3 Pool		All Treated Pool	
	M-V (N=295)	Comparator (N=289)	M-V (N=407)	Comparator (N=338)
Dyspnea	1 (0.3)	6 (2.1)	2 (0.5)	6 (1.8)
Dizziness	1 (0.3)	2 (0.7)	6 (1.5)	6 (1.8)
Paresthesia	1 (0.3)	1 (0.3)	5 (1.2)	2 (0.6)
Infusion site pain	0 (0.0)	0 (0.0)	18 (4.4)	9 (2.7)
Pruritus	0 (0.0)	2 (0.7)	0 (0.0)	4 (1.2)
Catheter site pain	0 (0.0)	0 (0.0)	7 (1.7)	4 (1.2)
Vessel puncture site bruise	0 (0.0)	0 (0.0)	7 (1.7)	3 (0.9)
Infusion site bruising	0 (0.0)	0 (0.0)	5 (1.2)	4 (1.2)
Catheter site bruise	0 (0.0)	0 (0.0)	5 (1.2)	4 (1.2)
Infusion site swelling	0 (0.0)	0 (0.0)	3 (0.7)	5 (1.5)
Catheter site swelling	0 (0.0)	0 (0.0)	3 (0.7)	5 (1.5)
Source: Applicant's Table 16, ISS ; and Clinical Reviewers' Analysis				

***Reviewers' Comment**: TEAEs that occurred in >1% patients in Phase-3 Pool are proposed to be included in the label by the Applicant.*

As mentioned earlier, headache and infusion related reactions were disproportionately higher in the mer-vab group as compared to comparator in Phase 3 Pool and All Treated Pool. Applicant excluded infusion site swelling, infusion site bruising, and catheter site reactions from the category 'infusion related reactions' justifying that those catheters were not used for study drug infusion.

Notably, there were two cases of chest discomfort which were directly associated with the infusion of study drug, however those are not accounted by the Applicant in infusion related reactions.

Subject #-703-005-508 in Study 505 was a 31-year-old white female with baseline CrCl >50, CSI score of 1, developed chest pressure of 'mild' severity while undergoing infusion on study day 1. This was considered as related to the study drug, however it resolved gradually and study drug was not withdrawn.
Subject # 503-003-520 was a 25-year-old black male healthy volunteer in Study 503. He started having chest discomfort while undergoing infusion on day 1, of 'mild' in severity. It resolved and study drug was not withdrawn. Same subject developed chest pain again on day 2 while undergoing infusion. It was 'moderate' in intensity leading to study drug withdrawal.

8.4.5.1. Adverse Events of Special Interest

TEAEs of special interest were defined based on adverse reactions associated with the use of meropenem including seizures, pseudomembranous colitis/CDAD, and hypersensitivity. No seizures were reported with meropenem-vaborbactam and the incidence of the other TEAEs of special interest was comparable across the treatment groups.

Seizure

Seizures were identified using the SMQ of convulsions. In both the Phase 3 and All Treated Pools, seizures were reported for no subject treated with mer-vab and 2 subjects (0.7%) treated with comparators. Both of these seizures were SAEs and occurred in Phase 3 Pool. One of these cases was considered severe, possibly related to the treatment with comparator, whereas the other case of seizure was considered unrelated to the comparator treatment. In both cases the SAEs were resolved.

***Reviewers' Comment**: This reviewer does not agree with the assessment of causality for the first case. On review of CRF, it is apparent that Patient # 840-005-505 with cUTI completed 15 infusions of piperacillin-tazobactam on study day 6 (* (b) (6) *without any complications. Patient was then transferred to long term care facility without any oral therapy. Note is written that physician discontinued the drug prematurely, as it was not felt to be clinically indicated. Seizure was reported on study day 11 (on day-5 post therapy). This patient's SAE of seizure in my assessment does not appear to be related to the study treatment.*

The second patient # 076-003-601 with cUTI in Study 506 with a significant medical history of supraventricular tachycardia, chronic renal failure on dialysis, bed ridden condition and recurrent bacteremia, developed SAE of seizure along with hypotension and sepsis on study day 3. This reviewer agrees with the causality of this case as not related to study treatment but due to patients' underlying disease.

Notably, no cases of seizures were reported in the mer-vab treatment group. Although there was a patient (#804-008-506 in Study 505), who developed an SAE of 'generalized tremor' and headache while receiving 9th infusion. This was considered moderate and has led to withdrawal of study drug.

Pseudomembranous colitis/ *Clostridium difficile*-associated diarrhea (CDAD)

Clostridium difficile is a major causative agent of colitis and diarrhea associated with the use of antibacterial drugs. For AEs potentially consistent with *C. difficile*- associated diarrhea, standardized MedDRA queries (SMQ) were performed using the preferred terms *C. difficile* diarrhea, antibiotic-associated colitis, *Clostridium difficile* colitis, clostridium colitis, and colitis

pseudomembranous.

The proportion of patients with TEAEs in the category of CDAD was low and similar in the mer-vab and comparator groups in Phase 3 Pool (1 patient [0.3%] in the mer-vab group and 3 patients [1.0%], in comparator group); and in All treated Pool (1 patient [0.2%] in the mer-vab and 3 patients [0.9%], in comparator group).

Hypersensitivity

The adverse event datasets for the meropenem-vaborbactam development program was searched for preferred terms related to hypersensitivity reactions. For this analysis, potential allergic reactions were recorded from the immune system disorder SOC, selected terms from the SOC skin and subcutaneous tissue disorders, gastrointestinal disorders, vascular disorders, injury/poisoning/ procedural, and nervous system disorders. Hypersensitivity was identified using three SMQs: anaphylactic reaction, angioedema, and hypersensitivity.

The proportion of subjects with hypersensitivity reactions was similar in the mer-vab and comparator groups in both Phase 3 Pool and All Treated Pool. All except one occurred in Phase-3 Pool. Table below present's AEs related to hypersensitivity reactions in the Phase-3 Pool by subject-ID, preferred term and its relatedness to study drug.

Table 86 Adverse Events Related to Hypersensitivity Reactions – Phase 3 and All Treated Pools, Safety Population

	Phase 3 Pool		All Treated Pool	
	Mer-vab N=295	**Comp N=289**	**Mer-vab N=407**	**Comp N=338**
	N, %	N,%	N, %	N,%
Anaphylactic reaction	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Urticaria	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Bronchospasm	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Contrast media reaction	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Drug hypersensitivity	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Hypersensitivity	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.3)
Rash	1 (0.3)	3 (1.0)	2 (0.5)	3 (0.9)
Dermatitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dermatitis contact	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.3)
Rhinitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Total	**7 (2.4%)**	**5 (1.7%)**	**11 (2.7%)**	**7 (2.1%)**
Source: Clinical Reviewer' Analysis; ISS				

Reviewers' Comment*: In the Phase 3 Pool, 7 (2.4%) patients in the mer-vab group and 5 (1.7%) patients in comparator group developed hypersensitivity reactions. In the All Treated Pool, 11 (2.7%) patients in the mer-vab and 7 (2.1%) patients in comparator group had an AE related to*

hypersensitivity reactions. The hypersensitivity reactions led to discontinuation of study medication in 2 patients (1 patient, # 505-703-005-512 with 'drug hypersensitivity' and another patient, # 505-703-001-502 with 'hypersensitivity') in the mer-vab group; and 3 patients in the comparator group (1 patient each with 'rash', 'hypersensitivity', 'drug hypersensitivity').

There were two additional patients identified in the mer-vab group with AE related to hypersensitivity reaction. Both were in Study 505. One patient (#604-004-502) had a life-threatening infusion-related reaction while undergoing infusion on study day 1, which led to discontinuation of study drug. It was assessed as serious and was considered probably related to study drug. A second patient (#804-001-507) had a severe infusion-related allergic reaction on study day 3 that led to discontinuation of the study drug. It was assessed as non-serious and was possibly related to study drug.

8.4.5.2. Adverse Drug Reactions

The Applicant has chosen the Phase 3 Pool to select adverse drug reactions (ADRs) for the package insert. ADRs were defined as all TEAEs assessed as related to the mer-vab and meeting one of the following three conditions: 1) known to be observed with the beta-lactam antibacterial drugs (e.g., gastrointestinal events, hypersensitivity reactions); 2) the incidence of the TEAE was greater in the mer-vab group than in the comparators group; or 3) there was biologic plausibility that the TEAE could be associated with meropenem-vaborbactam (e.g., injection site reactions, *Clostridium difficile* infections). Bacterial infections consistent with a lack of efficacy were excluded as ADRs. The Applicant also excluded catheter-related TEAEs as ADRs since the IV catheters associated with these events were not used for the infusion of study drug. ADRs known to be attributed to meropenem that were not identified in the meropenem-vaborbactam program were also selected.

Table below displays the frequent adverse drug reactions in the Phase 3 Pool that occurred in >1% of patients receiving mer-vab.

Table 87 Frequent adverse drug reactions in the Phase 3 Pool that occurred in >1% of patients receiving mer-vab (Safety Population)

Frequent adverse drug reactions in the Phase 3 Pool that occurred in >1% of patients receiving mer-vab		
	Phase 3 Pool	
	Mer-vab (N=295)	**Comparator* (N=289)**
	%	**%**
Any adverse drug reaction	42.7%	38.4%
Headache	8.8	4.2
Diarrhea	4.1	5.2
Infusion site reactions	3.7	0.7

Frequent adverse drug reactions in the Phase 3 Pool that occurred in >1% of patients receiving mer-vab		
	Phase 3 Pool	
	Mer-vab (N=295)	**Comparator* (N=289)**
Hypersensitivity**	2.7	2.1
Nausea	2.0	1.7
Alanine aminotransferase increased	1.7	0.3
Aspartate aminotransferase increased	1.4	0.7
Pyrexia	1.4	0.7
Vomiting	1.4	0.7
Abdominal distension	1.0	0.7

Source: Table 18, ISS
** hypersensitivity included the verbatim: hypersensitivity, drug-hypersensitivity, rash, urticaria, anaphylactic reaction, infusion-related reaction and bronchospasm;

** Comparators included piperacillin/tazobactam (n=273) and best available therapy (n=16), which includes use of the following IV antibiotics either in combination or alone for up to 14 days: carbapenem (meropenem, ertapenem, or imipenem), tigecycline, colistin, aminoglycosides (amikacin, tobramycin, or gentamicin), polymyxin B, and ceftazidime-avibactam (alone).

Reviewers' Comment*: For infusion site reactions, the Applicant has only included the terms 'infusion/injection site phlebitis', 'infusion site thromboses, and 'infusion site erythema'. Catheter site reactions were excluded when the catheters were not used for study drug infusion as noted by the Applicant. Other possible infusion related reactions including infusion site pain, infusion site bruising, and infusion site swelling, were excluded from consideration of infusion site reactions.*

The following adverse reactions were reported at a frequency below 1% with meropenem-vaborbactam:

Blood and lymphatic system disorders: leukopenia
General disorders and administration site conditions: chest discomfort
Infections and infestations: vulvovaginal candidiasis, oral candidiasis, Clostridium difficile colitis
Investigations: creatine phosphokinase increase
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: dizziness, tremor
Psychiatric disorders: hallucination
Renal and urinary disorders: incontinence
Vascular disorders: hypotension, phlebitis, vascular pain.

Other Adverse Reactions reported to be associated with Meropenem

Adverse reactions with a causal relationship to meropenem, identified by the Applicant from published literature,[45,46,47, 48] that were not reported in the clinical studies of mer-vab were as follows:

- *Blood and lymphatic system disorders*: thrombocytosis, neutropenia, eosinophilia, thrombocytopenia, agranulocytosis, hemolytic anemia,
- *Gastrointestinal disorders*: abdominal pain
- *Hepatobiliary disorders*: jaundice
- *Nervous system disorders*: paresthesia, convulsions
- *Investigations*: blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood bilirubin increased, blood creatinine increased, blood urea increased, blood thromboplastin decreased, prothrombin time decreased, direct and indirect Coombs test positive
- *Skin and subcutaneous tissue disorders*: pruritus, toxic epidermal necrolysis, Stevens Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome), erythema multiforme
- *Immune system disorders*: angioedema
- *General disorders and administration site conditions*: pain

8.4.6. Laboratory Findings

Laboratory testing was performed at pre-specified visit time points as outlined in Section 6.1.1. Laboratory results submitted in the ADLB datasets for study-505, study-506 and the ISS (for Phase 3 Pool and All Treated Pool) were analyzed. The proportions of patients with clinically significant changes from baseline were similar between treatment groups.

Hematology Tests Abnormalities

Few abnormalities in hematology tests which reported as TEAEs included anemia (5[1.4%] and 7 [1.7%]), leukopenia (1 [0.3%] each), and platelet count decreased (1 [0.3%] and 0%) in the

[45] Norrby SR, Gildon KM. Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem. Scand J Infect Dis. 1999;31:3-10.
[46] Linden P. Safety profile of meropenem: an updated review of over 6,000 patients treated with meropenem. Drug Saf. 2007;30(8):657-68.
[47] Baldwin CM, Lyseng-Williamson KA, Keam SJ. Meropenem a review of its use in the treatment of serious bacterial infections. Drugs. 2008;68:803-38.

[48] Mohr JF. Update on the efficacy and tolerability of meropenem in the treatment of serious bacterial infections. Clin Infect Dis. 2008;47 Suppl 1:S41-51. doi: 10.1086/590065.

mer-vab and comparator groups, respectively. None of these events was serious or led to study drug discontinuation.

In Study 505, 2 patients (0.7%) in the mer-vab group and 4 patients (1.5%) in the Pip-tazo group had an abnormality in a hematology parameter reported as an AE and all of these were anemia. Neither of the events of anemia in the mer-vab group was serious, required treatment, or resulted in discontinuation of study drug or the study.

Table below shows proportions of patients with clinically significant changes from baseline hematological values (Phase 3 Pool and All Treated Pool).

Table 88 Patients with Potentially Clinically Significant (PCS) Post-Baseline Abnormal Laboratory Values by Hematology Parameter (Phase 3 and All Treated Pools, Safety Population)

	Phase-3 Pool		All Treated Pool	
	M-V (N=295) n (%)	**Comparator (N=289) n (%)**	**M-V (N=407) n (%)**	**Comparator (N=338) n (%)**
Lab Test				
Red Blood Cells				
≤ 0.75 x LLN	5 (1.7)	9 (3.1)	6 (1.5)	9 (2.7)
≥1.25× ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White Blood Cells				
<2.0× 10^9/L	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
≥40× 10^9/L	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Absolute Neutrophil Count				
<1.0× 10^9/L	1 (0.3)	4 (1.4)	2 (0.5)	4 (1.2)
Absolute Lymphocyte Count				
<0.5× 10^9/L	6 (2.0)	2 (0.7)	6 (1.5)	2 (0.6)
Hematocrit				
≤ 0.75 x LLN	2 (0.7)	9 (3.1)	4 (1.0)	9 (2.7)
≥1.25× ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin				
≤ 115 g/L Male, ≤95 g/L Female	20 * (6.8)	26 (9.0)	21 (5.2)	26 (7.7)
≥180 g/L Male; ≥ 160 g/L Female	0 (0.0)	2 (0.7)	1 (0.2)	2 (0.6)
Platelet Count				
≤75 x 10^9/L	1 (0.3)	2 (0.7)	1 (0.2)	2 (0.6)
≥700 x 10^9/L	4 (1.4)	10 (3.5)	4 (1.0)	10 (3.0)
Source: ISS Table-44; and Clinical reviewers' Analysis **16 of these patients were in study-505*				

***Reviewers' Comment**: Overall rates of clinically significant changes in hematology values were similar between the treatment groups. The low proportion of clinically significant change in hematological parameters with mer-vab is plausible based on knowledge of the safety profile of*

meropenem and carbapenems, and with the short duration of therapy. Anemia has been observed in patients treated with meropenem, and thrombocytopenia has been reported with meropenem in patients with renal impairment, without reported clinical bleeding.

The slight decline in leukocytes in few patients would be expected clinically as patients with cUTI would be expected to have higher total leukocyte, and neutrophil counts at presentation, which should then decrease to normal with treatment. Of note, 2 patients in the mer-vab group reported having absolute neutrophil counts ≤1000. One patient in cUTI study- 505 (# 804-005-503) with a baseline absolute neutrophil count of 9,100, dropped to a count of 900 at EOIVT and EOT visit. Results returned to a normal value of 2,500 at TOC and 6,200 at LFU visit. Another patient in study-501 (# 02-02402) had an absolute neutrophil count of 2,500 at baseline, which dropped to 900 at Day 15 and returned to a normal count of 1,100 and 5,500 at EOS visit and follow up visits respectively.

Thrombocytopenia has been reported with meropenem use in patients with underlying renal insufficiency, however in meropenem-vaborbactam trials, incidence of thrombocytopenia was very low and comparable between groups. One explanation could be that patients there were very few patients with CrCl<30 in the Phase 3 Pool.

Assessment of Liver Function Tests

The Applicant has evaluated liver safety based on the FDA guidance for the detection of drug-induced liver injury[49]. The incidence of PCS (potentially clinically significant) liver test (LT) abnormalities was similar between the groups in the Phase 3 Pool at any time post-baseline up to the end of IV treatment (EOIVT). No patients presented with ALT ≥3X ULN or AST ≥3X ULN and total bilirubin ≥2X ULN, in the Phase 3 Pool or All Treated Pool. Mean changes from baseline over time in LTs were minimal and similar between the treatment groups in both Phase 3 Pool and All- treated Pool.

Elevations of alanine transaminase (ALT), and aspartate transaminase (AST) by 3-times, 5-times and 10-times the upper limit of normal, elevation of total bilirubin 2-times the upper limit of normal, and ≥50% increase in alkaline phosphatase for each arm by study visit for Phase-3 Pool and All Treated Pool is summarized in Table below.

[49] Food and Drug Administration. Guidance for Industry. Drug Induced Liver Injury: Premarketing Clinical Evaluation. 2009.

Table 89 Potentially Clinically Significant Liver Test Results (Phase-3 and All Treated Pools, Safety Population)

	Phase-3 Pool		All Treated Pool	
	M-V (N=295)	Comparator (N=289)	M-V (N=407)	Comparator (N=338)
Any Post Baseline Lab Test with PCS Abnormal	n (%)	n (%)	n (%)	n (%)
AST ≥20X ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST ≥10X ULN	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)
AST ≥5X ULN	3 (1.0)	3 (1.0)	3 (0.7)	3 (0.9)
AST ≥3X ULN	7 (2.4)	5 (1.7)	7 (1.7)	5 (1.5)
ALT ≥20X ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT ≥10X ULN	1 (0.3)	2 (0.7)	1 (0.2)	2 (0.6)
ALT ≥5X ULN	2 (0.7)	2 (0.7)	2 (0.5)	2 (0.6)
ALT ≥3X ULN	9 (3.1)	6 (2.1)	10 (2.5)	7 (2.1)
ALT or AST ≥20X ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT or AST ≥10X ULN	1 (0.3)	2 (0.7)	1 (0.2)	2 (0.6)
ALT or AST ≥5X ULN	4 (1.4)	3 (1.0)	4 (1.0)	3 (0.9)
ALT or AST ≥3X ULN	11 (3.7)	7 (2.4)	12 (2.9)	8 (2.4)
Potential Hy's Law cases:				
ALT or AST ≥3×ULN, TBIL ≥2×ULN, and ALP≤2×ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT or AST ≥3×ULN and TBIL ≥2×ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Modified from the Applicant's Table 25, ISS
ALT: Alanine transaminase; AST: Aspartate transaminase; EOIVT= end of intravenous treatment; PCS=potentially clinically significant; TBIL=total bilirubin; ULN = upper limit of normal N indicates number of subjects with at least one post-baseline assessment by EOIVT and with baseline non-PCS values.

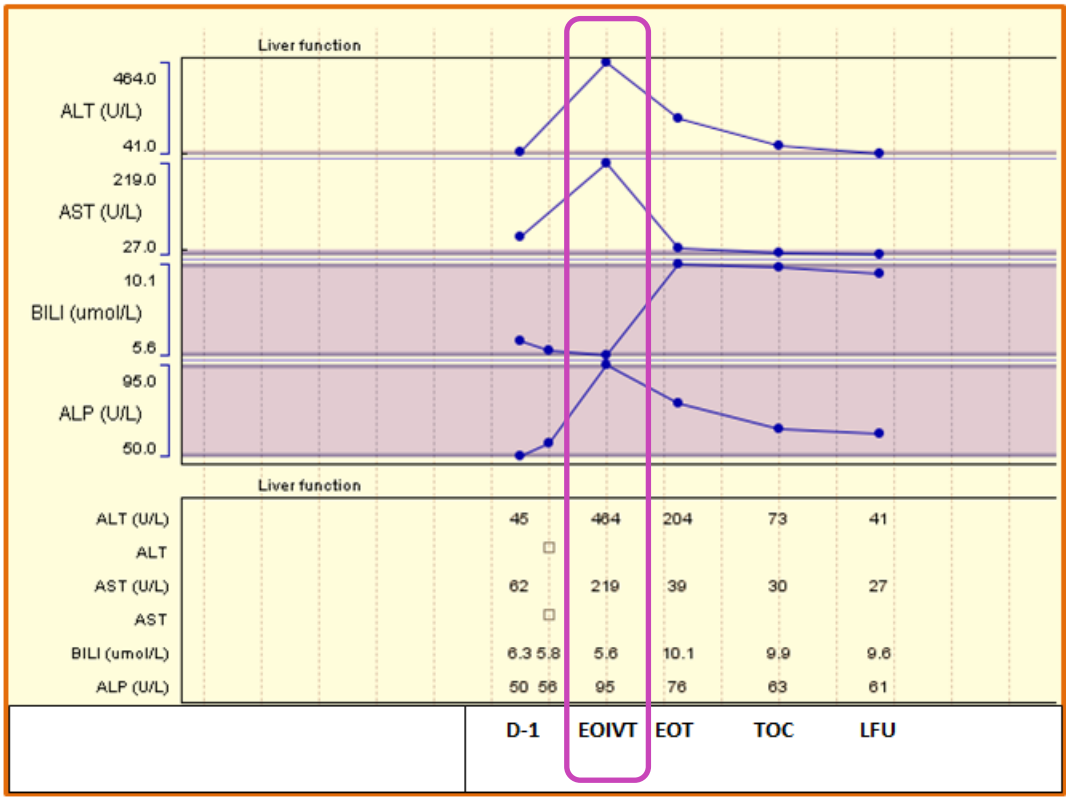
Abnormalities in other LTs that were reported as TEAEs in the meropenem-vaborbactam and comparator group, respectively, include ALT increased (6 [1.7%] and 2 [0.3%]), AST increased (4 [1.4%] and 2 [0.7%]), blood alkaline phosphatase increased (1 [0.3%] each), blood bilirubin increased (0 [0%] and 2[0.7%]), and transaminases increased (1 [0.3%] and 3 [1.0%]). None of these events were serious. An increase in serum bilirubin led to study drug discontinuation in 1 subject in the comparator group. There were no TEAEs or SAEs indicative of acute liver toxicity.

***Reviewers' Comment**: Both meropenem and vaborbactam are primarily excreted via the kidney and not metabolized in the liver. Hence, significant impact on the liver function tests is not anticipated. These results are consistent with prior observations with meropenem.*

Overall, there is no significant difference in the liver tests abnormalities. None of the patients met Hy's Law criteria or had ALT or AST ≥20X ULN. One patient in the mer-vab group (Patient #

505-804-001-518, shown in figure below) and 2 patients in comparator group (# 642-003-503 and # 804-005-519) had an elevation of ALT ≥10X ULN. All three patients were enrolled in Study 505.

Figure 7 Patient # 505-804-001-518 (ALT ≥10X ULN in mer-vab group)



Source: Clinical Reviewers' Analysis

***Reviewers' Comment**: The patient was an 18- year-old white male with AP, a Charlson comorbidity score ≤2, and no relevant medical history. Patients' concomitant medications included drotaverine hydrochloride, ketorolac, metamizole sodium, diphenhydramine, resorbilact, and paracetamol. At EOIVT, the patient had an increase in ALT from 45 U/L at baseline to 464 U/L (≥10X ULN; reference range, 6 U/L to 41 U/L) and an increase in AST from 62 U/L at baseline to 219 U/L (≥5X ULN; reference range, 9 U/L to 34 U/L). Total bilirubin at EOIVT was within the reference range (5.6 µmol/L; reference range, 1.7 µmol/L to 18.8 µmol/L). ALT and AST came down at EOT to 204 U/L and 39 U/L, respectively and further decreased to 73 73 U/L at TOC visit. At LFU visit, ALT returned to within the reference range (41 U/L). This patients' AEs of ALT increased and AST increased were reported starting on Day 7 and resolving on Day 19; both of these AEs were considered moderate, non-serious, and possibly related to study*

drug. The patient received 9 days of IV mer-vab, completed study treatment and study visits. The patient reportedly remained asymptomatic in terms of liver associated symptoms.

Two patients in the pip-tazo group had had ALT increase in ≥10X ULN. Patient # 642-003-504 received 7 days of IV piperacillin/tazobactam. Study drug was discontinued prematurely because of physician decision, prior to the event, as further treatment was not deemed clinically indicated. Increase in LFT occurred at LFU visit. The patient had an increase in ALT from 29 U/L at baseline to 615 U/L (≥10X ULN; reference range, 6 U/L to 41 U/L) and an increase in AST from 15 U/L at baseline to 412 U/L (≥10X ULN; reference range, 9 U/L to 34 U/L). Total bilirubin at LFU was within the reference range (18.8 µmol/L; reference range, 1.7 µmol/L to 18.8 µmol/L). One week after the LFU visit, ALT and AST had decreased to 119 U/L and 43 U/L, respectively, and returned to within reference range 2 weeks following LFU (25 U/L and 14 U/L, respectively). An AE of transaminases increased was reported starting on Day 21 and resolving on Day 35; this event was considered moderate, and non-serious.

The second patient # 804-005-519 was a 64- year-old, white male with cUTI with a non-removable source of infection and concurrent bacteremia, a Charlson comorbidity score ≥3, and no relevant medical history. The patient completed study treatment and the study visits. Relevant concomitant medications included tamsulosin hydrochloride, paracetamol, and ketorolac. The patient received 14 days of the comparator (because of bacteremia). On Day 3, the patient had an increase in ALT from 7 U/L at baseline to 482 U/L (≥10X ULN; reference range, 6 U/L to 41 U/L) and an increase in AST from 10 U/L at baseline to 349 U/L (≥10X ULN; reference range, 9 U/L to 34 U/L). Total bilirubin on Day 3 was within the reference range (13.5 µmol/L; reference range, 1.7 µmol/L to 18.8 µmol/L). At EOIVT, ALT and AST had decreased to 25 U/L and 14 U/L, respectively. AEs of ALT increased and AST increased were reported starting on Day 4 and resolving on Day 11 These events were considered severe, non-serious, and possibly related to the comparator.

Renal Function

The criteria used to define potentially clinically significant changes in renal function were increase in post baseline BUN values to ≥10.7 mmol/L and serum creatinine of ≥2.0 mg/dL (>=176.83 umol/L) during the study period.

Table 90 Potentially Clinically Significant Abnormal Renal Function Results (Phase-3 Pool and All Treated Pools)

	Phase-3 Pool		All Treated Pool	
	M/V (N=295) n(%)	Comparator (N=289) n (%)	M/V (N=407) n(%)	Comparator (N=338) n (%)

Lab Test Criteria				
BUN				
≥10.7 mmol/L	13 (4.4)	10 (3.5)	15 (3.7)	10 (3.0)
Cr				
≥2.0 mg/dL	0 (0.0)	6 (2.1)	1 (0.2)	6 (1.8)
Source: Table 26, ISS BUN=blood urea nitrogen; dL=deciliter; L=liter; mg=milligram; mmol=mill mole				

In the meropenem-vaborbactam group, no patients were reported to have a PCS post-baseline abnormal creatinine value whereas 6 patients (2.1%) in the comparator group had creatinine values ≥2.0 mg/dL.

Abnormalities in renal function that were reported as TEAEs in the Phase 3 Pool, in the mer-vab and comparator groups, respectively, included blood creatinine increased (0% in the mer-vab group and 0.7% in comparator group), blood urea increased (0% in the mer-vab group and 0.7% in comparator group), and decreased creatinine renal clearance (0.3% in the mer-vab group and 0% in comparator group). None of these events were serious. Blood creatinine increased led to study drug discontinuation in 1 patient in the comparator group. Consistent findings for renal function parameters were observed in the All Treated Pool.

Reviewers' Comment*: Of note, there was one patient in study-505 (# 804-009-524; 49 y/o, white male) in the mer-vab treatment group who had a TEAE of "azotemia," reported as an SAE of grade-3 (severe), and was considered not related to study drug. Patient also had a ureteric obstruction and oliguria. This patient had an underlying history of chronic kidney disease with a baseline CrCl < 30 ml/min. The TEAE started on study day 14, and was considered severe. It resolved by study day 22. This patients' concomitant medication were also reviewed, and none was listed, except for those started after the occurrence of this adverse event (which were sorbilact, neohemodez, pentoxyphylline, reosorbilact and dicynon). Table below present this patients' renal function values by study visits.*

Table 91 Renal Function Tests by Study Visits, Patient # 505-804-009-524

Renal Function Tests by Study Visits Patient # 505-804-009-524			
Study Day	*Creatinine Normal range [44-124]*	*Creatinine clearance Normal range [85-125]*	*BUN Normal range [1.79-7.85]*
Baseline	465	29	20.7
Day 3	416	33	17.9
End of IV Treatment	392	35	13.9
End of Treatment	392	35	13.9
Test of Cure	751	18	18.9
Late Follow-up	573	24	26.4

Reviewers' Comment*: Meropenem-vaborbactam is known to accumulate in patients with renal failure, and its dose needs to be adjusted, although the efficacy and safety of the modified dose is not tested in patients with severe renal failure (with CrCl<30 ml/min) in the Phase 3 trial.*

Other Serum Chemistry Parameters

The Applicants tables for high and low values for other chemistry parameters were also reviewed. In general, incidences of high and low values were similar across treatment groups. Few patients had potentially clinically significant changes in other serum chemistry parameters and the percentage of subjects with a PCS in each chemistry parameter was either similar in the two groups, except for decreased calcium, decreased potassium, and increased sodium which were higher in the comparator groups. In both Phase3 and All Treated Pools, mean changes in urinalysis parameters from baseline over time were minimal and similar between the treatment groups.

The abnormalities in other serum chemistry tests which were reported as TEAEs in the mer-vab and comparator groups, respectively, included hypokalemia (1.4% and 2.1%), hyperkalemia (0.3% each), blood creatinine phosphokinase increased (0.7% each), hypomagnesemia (0.7% and 0%), hypercholesterolemia (0.3% and 0%), hyperglycemia (0.3% and 0%), hypoglycemia (0.3% and 0%), and hypocalcemia (0% and 0.3%). None of these events were serious or led to study drug discontinuation. No urinalysis abnormalities were reported as TEAEs in the mer-vab or comparator group.

PCS changes in other chemistry results are displayed in table below.

Table 92 Potentially Clinically Significant Other Chemistry Results (Phase 3 and All Treated Pools, Safety Population)

	Phase 3 Pool		All Treated Pool	
	M-V (N=295) n (%)	**Comparator (N=289) n (%)**	**M-V (N=407) n (%)**	**Comparator (N=338) n (%)**
Calcium				
≤7.0 mg/dL	2 (0.7)	10 (3.5)	2 (0.5)	10 (3.0)
≥15.5 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CPK				
≥3.0 mg/dL	6 (2.0)	8 (2.8)	7 (1.7)	8 (2.4)
Glucose				
≤50 mg/dL	2 (0.7)	1 (0.3)	7 (1.7)	1 (0.3)
≥180 mg/dL	11 (3.7)	15 (5.2)	14 (3.4)	15 (4.4)
Potassium				
≤3.0 mmol/L	3 (1.0)	8 (2.8)	3 (0.7)	8 (2.4)
≥5.5 mmol/L	17 (5.8)	22 (7.6)	20 (4.9)	23 (6.8)

Sodium				
≤125 mmol/L	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
≥150 mmol/L	1 (0.3)	4 (1.4)	1 (0.2)	4 (1.2)
Source: Applicant's Table 27, ISS				

Reviewers' Comment*: Very few patients had potentially clinically significant changes in other serum chemistry parameters. However, there were proportionately higher number of patients with PCS change in chemistry parameters as compared to mer-vab group in both Phase-3 Pool and All treated Pool as shown in the table above.*

8.4.7. Vital Signs

Vital signs were recorded at baseline and at each study time point, in addition to unscheduled recordings. Both treatment groups were similar with regard to blood pressure fluctuations, and temperature changes. In the overall Safety Pool, 1 patient was reported as TEAE of bradycardia in comparator group. TEAE of hypertension, hypertensive crisis, or blood pressure systolic increase was reported in 6 patients, each group. Hypotension was reported in 2 patients in mer-vab group and 3 patients in comparator group. None of these TEAEs led to study drug discontinuation except 2 patients in comparator group, where study drug was discontinued in two patients, 1 each for hypotension and hypertension.

There were no clinically relevant differences in vital signs between mer-vab and comparators. The proportion of subjects with each potentially clinically significant vital sign was similar in the mer-vab and comparator groups. Consistent findings for systolic and diastolic blood pressure and pulse were seen in the All Treated Pool.

Table below presents proportion of subjects with each potentially clinically significant vital sign in the Overall Safety Population.

Table 93 Numbers (%) of Subjects with Potentially Clinically Significant (PCS) Post-Baseline Abnormal Vital Signs by Parameter (Phase 3 and All Treated Pool)

	Phase 3 Pool		**All Treated Pool**	
Vital Sign parameters	**Mer-vab N=295 n(%)**	**Comparator N=289 n(%)**	**Mer-vab N=407 n(%)**	**Comparator N=338 n(%)**
Respiratory Rate <= 10 rpm	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Respiratory Rate >=30 rpm	3 (1.0)	1 (0.3)	3 (0.7)	1 (0.3)
SBP <=90 mmHg and Decrease >=20 from Baseline	3 (1.0)	4 (1.4)	8 (2.0)	8 (2.4)
SBP >=180 mmHg and Increase >=20 mmHg from Baseline	3 (1.0)	3 (1.0)	7 (1.7)	4 (1.2)

DBP <=50 mmHg and Decrease >=15 mmHg from Baseline	6 (2.0)	5 (1.7)	17 (4.2)	12 (3.6)
DBP >=110 mmHg and Increase >=15 mmHg from Baseline	1 (0.3)	1 (0.3)	3 (0.7)	2 (0.6)
HR <=50 bpm and Decrease >=15 bpm from Baseline	0 (0.0)	0 (0.0)	5 (1.2)	5 (1.5)
HR >=120 bpm and Increase >=15 bpm from Baseline	3 (1.0)	3 (1.0)	3 (0.7)	3 (0.9)
Source: ISS, Table 14.5.3; and Table 14.5.4				

8.4.8. Electrocardiograms (ECGs)

During meropenem-vaborbactam trials, no subject discontinued treatment due to an ECG abnormality.

Heart Rate
The mean changes from baseline for heart rate were -2.4 and -8.2 bpm respectively for the mer-vab and pip-tazo treatment groups. In Phase 3 trial (Study 505), 3 patients (1%) in the mer-vab and 12 patients (5%) in the pip-tazo groups met bradycardic outlier criteria, and 7 patients (3%) in the mer-vab treatment group met tachycardia outlier criteria. These changes were of no clinical relevance. The time point analysis showed no clinically significant effect of Meropenem-vaborbactam on heart rate.

Reviewers' Comment*: The reviewer agrees that the decrease in heart rate observed were not clinically meaningful. These lowering of heart rate likely represent the decrease in heart rate which accompanies improvement in infection during successful treatment.*

PR and QRS
The changes in PR or QRS were of no clinical relevance. The mean changes from baseline for PR interval were 1.7 and 0.5 msec respectively for the mer-vab and pip-tazo treatment groups. Two subjects (1%) in the mer-vab group and 1 subject in the pip-tazo group met PR outlier criteria. The time point analysis showed no effect of mer-vab on the PR interval.

The mean changes from baseline for QRS duration were -0.6 and 0.4 msec respectively for the Mer-vab and pip-tazo treatment groups. These changes were of no clinical relevance. One subject in the mer-vab treatment group met QRS outlier criteria. The time point analysis likewise showed no effect of mer-vab on QRS duration.

QT
To judge the effects of mer-vab on cardiac repolarization, the Applicants' assessment was based on the corrected QT interval since heart rate inversely affects QT duration. The primary endpoint was the Fridericia's corrected QT (QTcF).

Two subjects (1%) in the mer-vab treatment group had a new QTcF >500 msec. Subject # 10007503, who had a left bundle morphology intraventricular conduction defect, had a baseline QTcF of 460 msec, which increased to a peak of 505 msec on Day 3, post-dose. Subject # 80405535, had a normal ECG at baseline, with a baseline QTcF of 456 msec, which increased at the End of IV Treatment to 500 msec pre-dose, and 505 msec post-dose.
One subject in the mer-vab group and 7 subjects (3%) in the pip-tazo treatment group had a QTcF >60 msec change from baseline. Subject # 158001507 in the mer-vab group had a baseline QTcF of 373 msec (at Screening) which increased to 441 msec post-dose at the End of IV Treatment time point.

***Reviewers' Comment**: This reviewer found 2 additional subjects in Study 501 who had a QT interval of >480 msec post treatment, which the Applicant has not mentioned. Subject # 501-02-02477 in cohort-5, who received meropenem 2g + vaborbactam 2 g , had a baseline QT of 445 msec, developed QT interval of 484 msec on Day 5 ; and subject # 501-02-02463 in cohort 4, who received RPX7009 2g + Meropenem 1g + vaborbactam 1 g had a baseline QT interval of 433 msec. He had a QT interval of 484 msec on Day-12, 4 hours post dose. However, none of the changes were clinically meaningful. Meropenem-vaborbactam did not cause meaningful ECG changes or concerns based on the submitted trials.*

8.4.9. QT

A thorough QT study was not conducted for Meropenem-vaborbactam. Prior to this NDA submission, under IND 120,040, the Applicant submitted a proposal for TQT waiver request. The FDA Interdisciplinary Review Team (IRT) for QT studies was consulted at that time, and recommendation was as follows: "Previous preclinical information, cardiovascular safety in clinical trials is not sufficient to rule out small increases in the QTc interval (<10 ms). A thorough QT study should be conducted according to the ICH E14 guidance." However, they further noted that the division may evaluate the safety data collecting from the existing clinical trials. If the division determines that the benefit overweighs the potential risk following the treatment of carbavance, the TQT assessment may be considered as part of the post-marketing requirement (PMR).

The Applicant has submitted a cardiac safety report summarizing findings related to cardiac safety from the non-clinical and clinical studies in the meropenem-vaborbactam development program. The objective of this report was evaluation of QT prolongation potential with administration of meropenem-vaborbactam combination product.

The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed the cardiac safety report. Please refer to the IRT-QT review for full details. In brief, overall ECG acquisition and interpretation of the study appeared acceptable with no clinically relevant effects on PR and QRS intervals. However, the studies in the current submission cannot be used to exclude small

effects (10 msec) as per the ICH E14 and ICH E14 Q&A (R3) guidelines. Therefore, the Applicant should conduct a TQT study for this product as a PMR to exclude small QT prolongation effects (10 msec threshold). The Applicant has not proposed any labeling language for QT effects.

8.4.10. Immunogenicity

Because meropenem and vaborbactam are small molecules and not peptides, immunogenicity was not anticipated and therefore not specifically evaluated in clinical trials, as immunogenicity is not a concern with the use of meropenem-vaborbactam for cUTI/AP.

8.5. Analysis of Submission-Specific Safety Issues

These were discussed in section 8.4.5.1- 'Adverse events of special interest'.

8.6. Safety Analyses by Demographic Subgroups

Factors with possible influence on TEAEs, including age, gender, race, renal impairment, Charlson comorbidity scores and SIRS were analyzed.

Subgroup analyses were performed for the Phase 3 and All Treated Pools as follows:

Demographic subgroups, including:

- Age (< 65 years old, ≥65 years old, and ≥75 years old);
- Gender: Male vs. Female;
- Race: White vs. Non-White (includes Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Aboriginal/Torres Strait Islander or Other Pacific Islander, Multiple, other);
- Ethnicity: Hispanic or Latino vs. Not Hispanic or Latino;
- Geographic Region: North America, Europe (includes Israel), and Rest of the World (includes Asia Pacific [Taiwan and Korea], Brazil, Peru, and Australia);
- In addition, the following baseline characteristics were summarized for the Phase 3 Pool;
- Diabetic status: Diabetic vs. Not diabetic;
- Creatinine clearance group: <30 mL/min, 30 to 50 mL/min and, >50 mL/min
- SIRS status: SIRS vs. Not SIRS
- Charlson comorbidity score: ≤2 vs. ≥3 and ≤5 vs. ≥6

No clinically relevant differences in the AE profile of meropenem-vaborbactam were seen for any of the subgroups.

8.6.1. Age

In the Phase 3 Pool, more than half of the patients in the mer-vab (195 or 66%) and comparator (179 or 62%) groups were <65 years of age. Approximately one-third of patients were ≥65 years of age (100 or 24% in the mer-vab group and 110 or 38.1% in the comparator group); Very few patients were ≥75 years of age (16% and 18%, respectively). The proportion of subjects with TEAEs, fatal TEAEs, SAEs, and TEAEs leading to either study drug or study discontinuation was lower in patients <65 years of age compared with patients ≥65 years of age or those ≥75 years of age. Similar results were seen in the All Treated Pool.

8.6.2. Gender

In the Phase 3 Pool, more females (191 or 64.7% in the mer-vab and 184 or 64% in the comparator group) than males (104 or 35% in the mer-vab and 105 or 36% in the comparator group) were enrolled. In the mer-vab group, the proportion of patients with SAEs was higher in males (12%) compared with females (4%).

A similar proportion of males and females reported TEAEs, drug-related TEAEs, fatal AEs, and TEAEs leading to study drug or study discontinuation. In the comparator group, a higher proportion of females reported TEAEs (42%) and drug-related TEAEs (17%) compared with males (32% and 11%, respectively).

In the All Treated Pool, TEAEs, fatal TEAEs, and TEAEs leading to study drug or study discontinuations occurred in a similar proportion of males and females in the mer-vab group; SAEs were reported by a higher proportion of males (8%) than females (4%). In the comparator arm, similar results were noted for males and females with the exception of a higher incidence in females of TEAES leading to study drug discontinuation or discontinuation from the study compared to males.

8.6.3. Race

In the Phase 3 Pool, the majority of patients were white, 275 (93%) in the mer-vab and 265 (92%) in comparator group. As less than 10% of patients were non-whites, 6.8% and 8.3%, in the mer-vab and pip-tazo group, respectively, no conclusions can be drawn when examining the incidence of TEAEs by race. Similar results were seen in the All Treated Pool. Similar results were observed for ethnicity in both pools.

8.6.4. Geographic Region

In the Phase 3 Pool, the majority of patients were from Europe, 261(89%) in the mer-vab and 251(87%) in comparator group. As less than 10% of patients were from either North America, (13 [4%] in the mer-vab and 16 [6%] in comparator group), or Rest of World, no conclusions can be drawn when examining the incidence of TEAEs by region. Similar results were seen in the All Treated Pool

8.6.5. Renal Function Status

Patients with severe renal impairment (CrCl <30 ml/min) were excluded from the Phase 3 trial (Study 505). Although this subgroup was not an exclusion criteria for Study 506, only 3 patients with CrCl<30 were enrolled in this trial. Therefore, total of 5 patients with CrCl <30ml/min were enrolled.

Table below presents the overall summary of TEAEs in the Phase 3 Pool and All Treated Pool by renal function status for the Phase 3 and All Treated Pools.

Table 94 Overall Summaries of TEAEs by Renal Function Status for the Phase 3 and All Treated Pools (Safety Population)

	Phase-3 Pool					
	Mer-vab (n= 295)			Comparator (N=289)		
	Creatinine Clearance n=290			**Creatinine Clearance n=285**		
	<30 (N=5) n (%)	≥30-50 (N=33) n (%)	>50 (N=252) n (%)	<30 (N=3) n (%)	≥30-50 (N=40) n (%)	>50 (N=242) n (%)
All TEAEs	4 (80.0)	18 (54.5)	102 (40.5)	2 (66.7)	18 (45.0)	89 (36.8)
Drug-related TEAEs	1 (20.0)	4 (12.1)	42 (16.7)	1 (33.3)	7 (17.5)	36 (14.9)
TEAEs leading to death	1 (20.0)	4 (12.1)	2 (0.8)	0 (0.0)	2 (5.0)	3 (1.2)
Subjects with SAE	3 (60.0)	5 (15.2)	12 (4.8)	1 (33.3)	4 (10.0)	13 (5.4)
Drug-related SAE	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.2)
TEAEs leading to study drug	0 (0.0)	4 (12.1)	6 (2.4)	2 (66.7)	3 (7.5)	11 (4.5)
TEAEs leading to study discontinuation	1 (20.0)	4 (12.1)	3 (1.2)	0 (0.0)	2 (5.0)	4 (1.7)
	All Treated Pool					
	Mer-vab (N=407)			Comparator (N=338)		
	Creatinine Clearance n=376			**Creatinine Clearance n=334**		
	<30 (N=20) n (%)	≥30-50 (N=37) n (%)	>50 (N=319) n (%)	<30 (N=3) n (%)	≥30-50 (N=40) n (%)	>50 (N=291) n (%)
All TEAEs	11 (55.0)	20 (54.1)	149 (46.7)	2 (66.7)	18 (45.0)	134 (46.0)
Drug-related TEAEs	5 (25.0)	6 (16.2)	76 (23.8)	1 (33.3)	7 (17.5)	66 (22.7)

TEAEs leading to death	1 (5.0)	4 (10.8)	2 (0.6)	0 (0.0)	2 (5.0)	3 (1.0)
Subjects with SAE	5 (25.0)	5 (13.5)	12 (3.8)	1 (33.3)	4 (10.0)	13 (4.5)
Drug-related SAE	1 (5.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	3 (1.0)
TEAEs leading to study drug	1 (5.0)	4 (10.8)	6 (1.9)	2 (66.7)	3 (7.5)	11 (3.8)
TEAEs leading to study discontinuation	1 (5.0)	4 (10.8)	3 (0.9)	0 (0.0)	2 (5.0)	4 (1.4)
Source: ISS, Clinical Reviewers' Analysis						

In the Phase 3 Pool, a higher incidence of TEAEs, deaths, SAEs, and TEAEs leading to study drug or study discontinuation was noted in patients with creatinine clearance ≥30 to 50 mL/min compared with those with creatinine clearance >50 mL/min in both mer-vab and comparator groups. As <10% of patients in either treatment group had a creatinine clearance <30 mL/min, no conclusions can be drawn when examining the incidence of TEAEs for this subgroup. Similar results were seen in the All Treated Pool.

***Reviewers' Comment**: When patients with CrCl<30 ml/min were tabulated by this reviewer, in the All Treated Pool, 13 out of 23 patients with CrCl<30ml/min had TEAEs. When looking at proportion of TEAEs, 11/20 (55%) patients in the mer-vab group (7 patients in Renal Insufficiency trial, Study 504 and 4 patients in Phase 3 trials) and 2/3 (67%) patients in the comparator group had any TEAEs. However, because of such a small numbers, no assessment could be made in this subgroup. The Applicant has proposed dose modification for patients with renal impairment, but has not demonstrated efficacy or safety of meropenem-vaborbactam in this clinically important subgroup of patients with moderate to severe renal insufficiency.*

TEAEs that occurred in patients with CrCl<30 ml/min in the mer-vab group were: diarrhea, headache, vomiting, abdominal pain, hemorrhagic diarrhea, metastatic prostate cancer, azotemia, oliguria, hematuria, rash, sepsis, pulmonary edema and anemia. TEAE that led to discontinuation of study drug was metastatic prostate cancer.

TEAEs occurred in this subgroup in the comparator arm were: blood creatinine increased, diarrhea, peripheral edema, tremor, pneumothorax, renal impairment and thrombocytopenia. The TEAEs of blood creatinine increased and renal impairment led to discontinuation of study drug.

TEAEs that were considered severe and related to study drug were diarrhea, headache, hemorrhagic diarrhea, and rash in the mer-vab group; none of these were serious. TEAE in the comparator group assessed as related to study drug was thrombocytopenia.

(Reader is referred to Appendix 13.11 for tabulated summary of TEAEs by PT in patients with CrCl<30 ml/min in the All Treated Pool).

Patients with creatinine clearance ≥30 to 50 mL/min and those with creatinine clearance >50 mL/min experienced the usually-encountered TEAEs (which were presented in section 8.4.5) in similar proportions in both groups.

A summary of TEAEs occurred in renal impairment trial, Study 504 is presented in the table below.

Table 95 Summary of TEAEs by Preferred Terms in Study 504

GROUP	TEAE- Preferred Term	SAE	Severity	Relatedness	Outcome
GROUP 2	Abdominal pain	N	Moderate	Related	RECOVERED
GROUP 5 (ESRD)	Abdominal pain	N	Mild	Not Related	RECOVERED
GROUP 1	Catheter site phlebitis	N	Mild	Not Related	RECOVERED
GROUP 2	Constipation	N	Mild	Not Related	RECOVERED
HEALTHY CONTROL	Hypersensitivity *	N	Mild	Not Related	RECOVERED
HEALTHY CONTROL	Hypersensitivity**	N	Mild	Not Related	RECOVERED
GROUP 5 (ESRD)	Diarrhea	N	Mild	Related	RECOVERED
GROUP 1	Diarrhea	N	Mild	Related	RECOVERED
GROUP 3	Diarrhea	N	Mild	Related	RECOVERED
GROUP 5 (ESRD)	Diarrhea hemorrhagic[ʃ]	Y	Severe	Related[+]	RECOVERED
GROUP 1	Headache	N	Mild	Not Related	RECOVERED
GROUP 1	Headache	N	Mild	Not Related	RECOVERED
GROUP 2	Headache	N	Mild	Related	RECOVERED
GROUP 5 (ESRD)	Headache	N	Mild	Related	RECOVERED
GROUP 5 (ESRD)	Muscle spasms	N	Mild	Not Related	RECOVERED
GROUP 5 (ESRD)	Paresthesia	N	Mild	Not Related	RECOVERED
GROUP 5 (ESRD)	Prostate cancer metastatic [ʃ]	Y	Severe	Not Related	N/A
GROUP 2	Rhinitis	N	Mild	Not Related	RECOVERED
GROUP 1	Sinus congestion	N	Mild	Not Related	RECOVERED
GROUP 5 (ESRD)	Skin injury	N	Mild	Not Related	RECOVERED
GROUP 2	Vessel puncture site hematoma	N	Mild	Not Related	RECOVERED
GROUP 5 (ESRD)	Vomiting	N	Mild	Not Related	RECOVERED

Source: Clinical Reviewer' Analysis;
GROUP1= Mild Renal Insufficiency; GROUP2= Moderate Renal Insufficiency; ESRD: End Stage Renal Disease;

**Subject # 05-623, healthy volunteer, developed contact dermatitis described as maculopapular rash with erythema in the right antecubital region on Day 1 and diagnosed at the Day 3 physical examination; this observation was recorded as Abnormal-Clinically Significant and reported as an AE. Topical hydrocortisone cream (1%) was prescribed QID/as needed for contact dermatitis from 24-Apr-14 through 26-Apr-14. Rash and erythema resolved on 27-Apr-14 and were deemed Not Related by investigator.*

***Subject # 05-631, healthy volunteer, received single dose of study drug on 05-Jun-14 and developed contact dermatitis at ECG pad sites on 06-Jun-14. Topical hydrocortisone cream*

(1%) treatment was prescribed TID/as needed, which began 07-Jun-14 and ended when the contact dermatitis resolved, on 10-Jun-14. Contact dermatitis was considered Not Related to study drug by Investigator;
ʃ SAEs.
+ Not related per this reviewers' assessment

***Reviewers' Comment**: Despite the majority of TEAEs reported as mild and not related to study drug, higher proportions of subjects with ESRD had adverse events, and one of those was considered serious, severe in intensity and led to discontinuation of study drug.*

Reader is referred to section 8.4.2 for narrative of Case # 504-05-634 (Hemorrhagic Diarrhea).

Another SAE that was not related to study drug however, led to discontinuation of study was metastatic prostate Cancer. Subject # 05-637, in ESRD group, received one dose of study drug prior to his dialysis run on 25 July 2014 and was due to receive a second dose on 1 August 2014; however, he experienced lower back and right hip pain that worsened and required hospitalization on (b) (6) He had chronic hip pain since then and initially blamed his current symptoms on that. An MRI was performed on (b) (6) showing some bone "lesions". A T12 laminectomy and a T11-L1 posterior fusion were performed on (b) (6). During the procedure, a biopsy was collected that came back positive for metastatic prostate cancer. A bone scan was performed that showed activity in the right ilium, T12 vertebra, and right 7th rib. Subject was diagnosed with metastatic prostate cancer with bone metastases. No further details available on treatment or outcome. The SAE of metastatic prostate cancer was considered Not Related to study drug by Investigator.

Given the small number of subjects with severe renal impairment in the meropenem-vaborbactam trials, ongoing pharmacovigilance is required to detect low-frequency events that may not be observed with this sample size.

8.6.6. Diabetic Status

In the Phase 3 Pool, a higher incidence of TEAEs, drug-related TEAEs, deaths, SAEs, and TEAEs leading to study drug or study discontinuation was noted in diabetic patients as compared to patients without diabetes in both the mer-vab and comparator groups.
In the All Treated Pool, diabetic status was not examined as many subjects were healthy volunteers.

Table below presents TEAEs occurring in Phase 3 Pool based on diabetic status.

Table 96 TEAEs occurring in Phase 3 Pool based on diabetic status

	Mer-vab (n=295)		Comparator (N=289)	
	Diabetic N=50 (17%) n (%)	**Not Diabetic N=245 (83%) n (%)**	**Diabetic N=51 (18%) n (%)**	**Not Diabetic N=238 (82%) n (%)**
All TEAEs	26 (52.0)	100 (40.8)	28 (54.9)	83 (34.9)
Drug-related TEAEs	6 (12.0)	41 (16.7)	11 (21.6)	33 (13.9)
TEAEs leading to death	4 (8.0)	3 (1.2)	3 (5.9)	2 (0.8)
Subjects with SAE	5 (10.0)	15 (6.1)	7 (13.7)	11 (4.6)
Drug-related SAE	0 (0.0)	1 (0.4)	2 (3.9)	1 (0.4)
TEAEs leading to study drug discontinuation	4 (8.0)	6 (2.4)	6 (11.8)	10 (4.2)
TEAEs leading to study discontinuation	4 (8.0)	4 (1.6)	3 (5.9)	3 (1.3)

***Reviewers' Comment**: Although distributions of diabetic patients were comparable between the two treatment groups, there were only about 17% of patients with diabetes treated with meropenem-vaborbactam in Phase 3 trials. Higher incidence of TEAEs in diabetic patients will be expected, as mentioned earlier; diabetic patients are at higher risk of developing cUTI, complicated pyelonephritis and its complications. Various impairments in the immune system, poor metabolic control, and incomplete bladder emptying due to autonomic neuropathy may all contribute to the enhanced risk of urinary tract infections and its complications in these patients. Serious complications of UTI are encountered more frequently in type 2 diabetes than in the general population. In addition, these patients are more prone to have resistant pathogens as the cause of their UTI, including extended-spectrum β-lactamase-positive Enterobacteriaceae[50], and carbapenem-resistant Enterobacteriaceae[51].*

8.6.7. Systemic Inflammatory Response Syndrome (SIRS) Status

In the Phase 3 Pool, a higher incidence of TEAEs and deaths was noted in patients with SIRS compared to those without SIRS in both mer-vab and comparator groups. The incidence of drug-related TEAEs was also higher in patients with SIRS compared to patients without SIRS in

[50] Inns T, Millership S, Teare L, Rice W, Reacher M. Service evaluation of selected risk factors for extended-spectrum beta-lactamase Escherichia coli urinary tract infections: a case-control study. J Hosp Infect. 2014;88(2):116–119

[51] Schechner V, Kotlovsky T, Kazma M, et al. Asymptomatic rectal carriage of blaKPC producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected? Clin Microbiol Infect. 2013;19(5):451–456

the mer-vab group. The SIRS status was not examined in the All Treated Pool as many subjects were healthy volunteers.
Table below shows the proportions of patients with TEAEs based on SIRS status.

Table 97 TEAEs based on SIRS status (Phase 3 Pool)

	Phase 3 Pool			
	Mer-vab (N=295)		Comparator (N=289)	
	SIRS N=85 (29%)	**Not SIRS N=210 (71%)**	**SIRS N=98 (34%)**	**Not SIRS N=191 (66%)**
	n (%)	n (%)	n (%)	n (%)
All TEAEs	41 (48.2)	85 (40.5)	40 (40.8)	71 (37.2)
Drug-related TEAEs	19 (22.4)	28 (13.3)	16 (16.3)	28 (14.7)
TEAEs leading to death	3 (3.5)	4 (1.9)	4 (4.1)	1 (0.5)
Subjects with SAE	6 (7.1)	14 (6.7)	10 (10.2)	8 (4.2)
Drug-related SAE	0 (0.0)	1 (0.5)	1 (1.0)	2 (1.0)
TEAEs leading to study drug discontinuation.	3 (3.5)	7 (3.3)	6 (6.1)	10 (5.2)
TEAEs leading to study discontinuation	3 (3.5)	5 (2.4)	5 (5.1)	1 (0.5)
Source: ISS, Table 35				

***Reviewers' Comment**: Overall, there were low numbers (about 30%) of patients presented with SIRS in the mer-vab Phase 3 trials. However, proportions of patients with SIRS were similar between the treatment groups. Presence of SIRS in cUTI/AP patients would suggest higher severity of infection than those without SIRS. Incidence and severity of TEAEs were similar in patients with or without SIRS in the mer-vab Phase 3 trials as shown in table above.*

8.6.8. Charlson Comorbidity Score (CCS)

The Charlson comorbidity score was not examined in the All Treated Pool as many subjects were healthy volunteers. In the Phase 3 Pool, a higher incidence of TEAEs, drug-related TEAEs, deaths, SAEs, drug related SAEs and TEAEs leading to study drug or study discontinuation was noted in both treatment groups for patients with a CCS ≥6 versus those with a score ≤5.
Table below presents an overall summary of TEAEs by Charlson Comorbidity Score (≤5 versus ≥6) for the Phase 3 Pool (Safety Population).

Table 98 TEAEs by Charlson Comorbidity Score (≤5 versus ≥6) for the Phase 3 Pool (Safety Population)

	Mer-vab (N=295)		Comparator (N=289)	
	CCS ≤5 ; N=252 n (%)	***CCS ≥6; N=43 n (%)***	***CCS ≤5 ; N=235 n (%)***	***CCS ≥6; N=54 n (%)***
All TEAEs	98 (38.9)	28 (65.1)	83 (35.3)	28 (51.9)
Drug-related TEAEs	36 (14.3)	11 (25.6)	32 (13.6)	12 (22.2)
TEAEs leading to death	3 (1.2)	4 (9.3)	1 (0.4)	4 (7.4)
Subjects with SAE	12 (4.8)	8 (18.6)	8 (3.4)	10 (18.5)
Drug-related SAE	1 (0.4)	0 (0.0)	0 (0.0)	3 (5.6)
TEAEs leading to study drug discontinuation	5 (2.0)	5 (11.6)	12 (5.1)	4 (7.4)
TEAEs leading to study discontinuation	4 (1.6)	4 (9.3)	2 (0.9)	4 (7.4)
Source: ISS, Table 37;				

Reviewers' Comment*: Overall, In Study 505 (pivotal cUTI study), the number of patients with higher Charlson comorbidity score (CCS ≥6) was lower as compared to Study 506.*

While comparing two treatment groups in the Phase 3 trials, proportions of patients with CCS ≥6 were slightly lower the mer-vab group as compared to the comparator group (43/295, 15% in the mer-vab, and 54/289, 19% in comparator group). When looking at TEAEs by preferred terms, patients in both groups experienced the usually-encountered TEAEs as discussed in section 8.4.5.

As would be expected, incidences of TEAEs, drug related TEAEs, TEAEs leading to study drug discontinuations, were higher in patients with CCI score ≥6 as compared to patients with CCI score ≤5 in both treatment groups.

8.7. Specific Safety Studies/Clinical Trials

8.7.1. Drug-Drug Interactions

Based upon available in vitro and in vivo data, meropenem and vaborbactam both have a low potential for metabolic drug-drug interactions. Meropenem is hydrolyzed to an inactive metabolite which accounts for approximately 28% of a dose eliminated via the urine ([MERREM® IV USPI, 2016]. Vaborbactam does not undergo metabolism based on Applicants' clinical pharmacology studies (Reader is referred to the FDA Clinical pharmacologist Review for additional details).
In vitro studies show a low potential for inhibition or induction of key enzyme systems (e.g., CYPs). Meropenem has been identified as having a potential for reduced drug clearance with

co-administration of probenecid. Reduced metabolism of valproic acid has been reported with several carbapenems, including meropenem. Both of these interactions are described in prescribing information for meropenem ([MERREM® IV USPI, 2016].

Probenecid

Meropenem has been identified as having a potential for reduced drug clearance with co-administration of probenecid. Probenecid is a well-established inhibitor of organic anion transporters, and can reduce the clearance of many beta-lactam drugs undergoing tubular secretion, including carbapenems. Given the potential to reduce meropenem clearance, probenecid is not recommended for use in patients receiving meropenem or meropenem-vaborbactam.

Valproic Acid

A significant PK drug-drug interaction in humans with valproic acid has been described with several of the carbapenems, including meropenem. Co-administration results in rapid reduction in serum valproic acid concentrations, which has often resulted in lower efficacy of valproic acid and breakthrough seizures. Valproic acid undergoes glucuronidation in the liver. Inhibition of a hydrolase responsible for converting valproic acid-glucuronide to valproic acid conversion in the liver has been implicated as the mechanism for reduced valproic acid serum levels with concomitant carbapenem administration.[52] Given the reduction in valproic acid levels and the potential for seizure activity, the combination of valproic acid and meropenem or meropenem-vaborbactam is not recommended. If administration of meropenem-vaborbactam is necessary, then supplemental anti-convulsant therapy should be considered.

8.7.2. Drug-Disease Interactions

Renal

The overall safety data presented in this NDA application did not show any evidence of renal toxicity with meropenem-vaborbactam. In Renal Impairment study (Study 504), conducted in subjects with renal insufficiency and subjects receiving hemodialysis, meropenem-vaborbactam was safe and well tolerated in patients with end-stage renal disease; however, a higher number of AEs were observed when study drug was administered after dialysis as opposed to before dialysis.

[52] Masuo Y, Ito K, Yamamoto T, Hisaka A, Honma M, Suzuki H. Characterization of Inhibitory Effect of Carbapenem Antibiotics on the Deconjugation of Valproic Acid Glucuronide. Drug Metab Dispos; 2010;38:1828-35.

Reviewers' Comment*: The current meropenem label states that dosage should be reduced in adult patients with renal impairment [MERREM® IV USPI, 2016]. Dose reductions are also proposed by the Applicant for the use of meropenem-vaborbactam in patients with renal impairment. However, as mentioned earlier, safety and efficacy of meropenem-vaborbactam has not been evaluated in patients with creatinine clearance <30.*

Hepatic

The overall safety data presented in this NDA did not show any evidence of liver injury or hepatic safety signals associated with meropenem-vaborbactam combination. The meropenem label states that no dosage adjustment is necessary in patients with impaired hepatic function [MERREM® IV USPI, 2016].

8.7.3. Safety Data from Healthy Subjects

Safety data for healthy subjects in the Phase 1 trials in the meropenem-vaborbactam clinical development program are presented as part of the All Treated Pool in section 8.6. Meropenem-vaborbactam was generally well tolerated by healthy volunteers. No SAEs were reported in these subjects. In Phase 1 trials, common adverse events outside of infusion site/catheter site events were limited to headache, lethargy, dizziness, nausea, and diarrhea.

Reviewers' Comment*: One subject in Study 501, who received meropenem 1 g +vaborbactam 2 g, discontinued study drug due to a TEAE of thrombophlebitis. Another subject in Study 503, who received the proposed dose of meropenem 2 g - vaborbactam 2 g, discontinued study drug due to a TEAE of chest discomfort.*

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There are no concerns with human carcinogenicity with meropenem-vaborbactam, given its antibacterial class and short treatment duration. There are no human data available for carcinogenicity or tumor development with Meropenem-vaborbactam.

Reviewers' Comment*: Based on the available data from Phase 1 and Phase 3 trials, there is no clinical evidence of carcinogenicity for the Meropenem-vaborbactam combination regimen. Four patients in overall safety population (3 patients in Study 505, and 1 patient in Study 504)*

experienced an event within the SOC of Neoplasms, Benign, Malignant, and Unspecified. Two of those neoplasms were colon cancer (1 in the mer-vab [# 505-616-003-507] and 1 patient in comparator group [# 505-804-008-505]); 1 patient in the mer-vab group (# 505-642-003-503) had an event of rectal neoplasm, and 1 patient (# 504-05-637 in Renal Impairment Study in the mer-vab group) had an event of metastatic prostate cancer. None of the events were related to study drug.

8.8.2. Human Reproduction and Pregnancy

In the Phase 3 trials, all women of child-bearing age were required to undergo a serum or urine pregnancy test before enrollment and were required to use contraception for the duration of the study period. No human studies have investigated the potential effects of meropenem-vaborbactam during pregnancy and lactation. Animal studies have shown no potential for teratogenicity and no effects on fertility or reproductive parameters.

One patient (# 112-004-506) in the mer-vab group in Study 505 was discontinued from the study after receiving 7 doses of study drug over 3 days when her serum pregnancy test collected on Day 1 came back positive. No AEs were reported in this patient; the pregnancy was terminated by an elective abortion 7 days later.

<u>Case Narrative (patient #112-004-506)</u>

The patient # 112-004-506 was a 21-year-old female, who was enrolled in Study 505 with cUTI. Starting on 21 Oct 2015, the patient was randomized to meropenem-vaborbactam and received 7IV infusions of meropenem-vaborbactam over a period of 3 days. The patients' baseline urine pregnancy test was negative; On Day 3 (23 Oct 2015), laboratory assessment of blood chemistry revealed that the patient was pregnant (β-HCG 1236 IU/L).

During the treatment period, the patient continued taking the following medications (From 21 Oct 2015 to 26 Oct 2015): drotaverine, fenpiverinium bromide with metamizole, diphenhydramine, and papaverine. Vital signs showed temperature 36.6ºC, blood pressure 112/80 mmHg, heart rate 76 bpm, and respiratory rate 18 breaths per minute. Laboratory assessment of hematology and additional blood chemistry revealed the following results outside the normal range: erythrocyte mean corpuscular hemoglobin concentration 316 g/L, hemoglobin 118 g/L, amylase 34 U/L, bicarbonate 20 mmol/L, creatinine clearance 132 mL/min, phosphate 0.71 mmol/L, and urate 149 µmol/L.
Study drug was discontinued due to the pregnancy. Follow-up assessment revealed that the patient elected termination at gestational age 6 weeks. The elective termination was not caused by any medical reason and there were no complications, infections, or illnesses during the pregnancy.

8.8.3. Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of meropenem-vaborbactam in pediatric patients (younger than 18 years of age) has not been studied.

The Applicant has not requested waivers in any of the age groups of the pediatric population. The Applicant has requested deferral for pediatric studies in children from birth to less than 18 years. Pediatric Study Plan was agreed between the Agency and the Applicant on December 2, 2015.

Proposed Pediatric Clinical Studies

The pediatric development program includes the following three clinical studies in pediatric subjects in all age groups (birth to < 18 years of age):

i) **Study 507**: A Phase 1, open-label, dose-finding, single-dose, PK, safety, and tolerability study of meropenem/RPX7009 in pediatric subjects (birth to < 18 years) with (b) (4) bacterial infections (b) (4)

ii) (b) (4) A Phase 2, randomized, single-blind, active comparator study to evaluate the safety, tolerability, and PK of meropenem/RPX7009 versus piperacillin/tazobactam for the treatment of pediatric subjects from 3 months to < 18 years of age with cUTI (including AP).

iii) (b) (4) A Phase 2, open-label, active comparator study to evaluate the safety, tolerability, and PK of multiple dose infusions of meropenem/RPX7009 versus comparator in neonates (≤ 90 days of age) with late-onset sepsis, (b) (4)

The planned pediatric study plan is outlined in the table below.

Table 99 Nonclinical and Clinical Studies for Meropenem-vaborbactam

PLANNED NONCLINICAL STUDIES			
Species	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
(b) (4)			N
			N
PLANNED CLINICAL STUDIES			
Pediatric PK, Safety, and Tolerability Studies			
Study/Age Group	**Type of Study**	**Comments**	**Deferral Request Planned for the**

			Study (Y/N)
Study 507 / Birth to < 18 years	Phase 1, PK, safety, tolerability study	To evaluate safety, tolerability, and PK of a single IV dose	Y
Clinical Safety, Tolerability and PK Studies			
Study/Age Group	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
(b) (4) / 3 months to < 18 years	Phase 2, safety, tolerability, and PK study (R, SB, C)	To assess safety, tolerability, and PK. Efficacy endpoints will also be assessed.	Y
(b) (4) / Birth to ≤ 90 days	Phase 2, safety, tolerability, and PK study (OL, C)	To assess safety, tolerability, and PK. Efficacy endpoints will also be assessed.	Y
C: comparator; GLP: Good Laboratory Practices; OL: Open label; PK: pharmacokinetics; R: randomized; SB: single blind.			

The Applicants' justification for deferral of pediatric studies

The Applicant is requesting a deferral for the following:

- (b) (4)

- [redacted]

One pediatric trial, Study 507, is ongoing and two trials [redacted] are planned.

The projected date for the submission of the pediatric studies is projected as follows:

Projected Date until Submission Studies Would be Deferred			
Description	***EDC***	***EDFRS***	***Other Dependency***
Study 507: Phase 1,dose-finding PK study in infants, children, and adolescents <18 years of age	3Q2019	1Q2020	[redacted]
[redacted] Phase 2, safety, tolerability, and PK study in children 3 months to <18 years of age	3Q2021	1Q2022	[redacted]
[redacted] Phase II study in sepsis in neonates from birth to <3 months of age	4Q2024	2Q2025	[redacted]
EDC= Estimated date of completion; EDFRS: Estimated date of final report submission; GLP=Good Laboratory Practices; PK=pharmacokinetics			

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdosage

Out of 407 subjects treated with meropenem-vaborbactam in the clinical development program, there was no incidence of accidental overdose of meropenem-vaborbactam. In the event of overdosage, the Applicant recommends to discontinue meropenem-vaborbactam and institute general supportive care.

Limited post-marketing experience with meropenem indicates that if AEs occur following overdosage, they are consistent with the known AE profile and are generally mild in severity and resolve on withdrawal or dose reduction [MERREM® IV USPI, 2016].

Studies show that both meropenem and vaborbactam are readily dialyzable and effectively removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdosage.

Abuse and Dependency

No animal studies have been conducted evaluating the abuse potential of meropenem-vaborbactam. However, there is no pharmacologic evidence to suggest an abuse potential for meropenem-vaborbactam and drug abuse and dependence is not expected with this class of drugs. None of the AEs in the clinical development program were suggestive of drug dependence.

Withdrawal or Rebound

No evidence of a withdrawal or rebound effect was noted after meropenem-vaborbactam treatment was completed or stopped.

Effects on Ability to Drive or Operate Machinery

No specific nonclinical or clinical studies were performed to evaluate the potential for Meropenem-vaborbactam to impair the senses or coordination or any other factor that would result in a diminished ability to drive a vehicle, operate machinery, or impair mental ability. However, there is no pharmacologic evidence to suggest such effects.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Meropenem-vaborbactam combination product is not marketed in any country.

Meropenem

Meropenem was approved in the US in 1996, under the proprietary name of Merrem IV and multiple generic versions are available and is most frequently dosed at 500 mg or 1 g every 8 hours (although it is approved at doses up to 2 g every 8 hours in patients with certain

infections) [MERREM® IV USPI, 2016]. The United States Package Insert (USPI) for Merrem IV includes the following local and systemic adverse clinical reactions that were reported irrespective of the relationship to meropenem IV (occurring in >1.0% of the patients): diarrhea (4.8%), nausea/vomiting (3.6%), inflammation at the injection site), headache (2.3%), rash (1.9%), sepsis (1.6%), constipation (1.4%), apnea (1.3%), shock (1.2%), and pruritus (1.2%) [MERREM® IV USPI, 2016].

The Summary of Product Characteristics (SPC) from the EMA states that meropenem-related adverse reactions most frequently reported were diarrhea (2.3%), rash (1.4%), nausea/vomiting (1.4%) and injection site inflammation (1.1%) [Meronem IV SmPC, 2016]. The most commonly reported meropenem-related laboratory AEs were thrombocytosis (1.6 %) and increased hepatic enzymes (1.5% to 4.3 %).

In a review of over 6000 patients treated with meropenem (most frequently dosed at 500 mg or 1 g every 8 hours), the most common AEs reported were diarrhea (2.5%), rash (1.4%) and nausea/vomiting (1.2%).[53]

Vaborbactam

Vaborbactam is not marketed in any country either alone or with any other drug.

8.9.2. Expectations on Safety in the Postmarket Setting

Reviewers' Comment*: Safety analyses and conclusions in this review are primarily based upon known safety profile of meropenem, and data from the submitted Phase 3 trial on meropenem-vaborbactam combination. Safety in the postmarket setting can be managed by routine pharmacovigilance activities. The eligibility criteria for the pivotal trial may mitigate potential safety concerns that may be observed with wider usage in the postmarket setting. Emergence of new events can be managed by routine pharmacovigilance activities.*

No major safety signals were identified in overall safety data base of Meropenem-vaborbactam.

8.10. Additional Safety Issues From Other Disciplines

There are no additional safety issues from other disciplines that are not presented elsewhere in this review.

[53] Linden P. Safety profile of meropenem: an updated review of over 6,000 patients treated with meropenem. Drug Saf. 2007;30(8):657-68.

8.11. Integrated Assessment of Safety

No new safety issues unique to mer-vab have been identified that merit inclusion in labeling.

Meropenem-vaborbactam is the combination of the approved carbapenem antibacterial meropenem, and the investigational beta-lactamase inhibitor vaborbactam. The analysis of safety of mer-vab in the treatment of cUTI/AP is based on known, favorable safety profile of meropenem for other approved indications, along with in vitro, in vivo and clinical safety data from 337 patients exposed to proposed dose of mer-vab. There was no suggestion from this review that addition of vaborbactam exacerbated the toxicity potential of meropenem. There were no major safety issue(s) identified in this review and overall review suggests that mer-vab has a relatively favorable safety profile.

Preclinical Safety

Although vaborbactam, like meropenem, is primarily renally excreted there was no evidence of any renal toxicity, either in a single agent toxicology studies or combination toxicology studies, in any of the toxicology species. Unlike meropenem, which has a metabolite called hydrolyzed meropenem, vaborbactam is metabolically stable in vitro and after in vivo administration. About 90% of vaborbactam administered to rats is recovered unchanged in urine. Vaborbactam also has no meaningful activity as an inducer or an inhibitor of CYP450 enzymes, and no activity as an inhibitor or substrate of drug transporters. Collectively data suggest a very low potential for vaborbactam to impact the disposition of other concomitantly administered drugs.

Vaborbactam has favorable safety profile with no effect on the core organ systems (respiratory, cardiovascular and central nervous system) in vivo safety pharmacology studies and was very well tolerated in general toxicology studies in both Sprague Dawley rats and Beagle dogs. Vaborbactam was evaluated as a single agent in range finding and GLP repeat-dose toxicology studies for up to 14 days, and by itself and in combination with either meropenem or biapenem, another carbapenem, for 28 days, some with a 28-day recovery period. There was no systemic toxicity of vaborbactam and no kinetic or toxicologic interaction between vaborbactam and meropenem. No-observed-adverse-effect-levels NOAELs in all the toxicology studies were the highest doses of vaborbactam administered by itself (1000 mg/kg/day), the highest doses of meropenem administered by itself (500 mg/kg/day) and the highest doses of vaborbactam administered in combination with meropenem (1000 mg/kg/day and 500 mg/kg/day, respectively). Exposure (AUC) to vaborbactam, meropenem and the metabolite of meropenem that were achieved in the toxicology studies of mer-vab at the highest dose levels tested, which are also the NOAELs, are 2-7-fold the daily AUC achieved in humans when vaborbactam is

administered in combination with meropenem at a combined dose of 2000 mg for each entity and infused over a 3- hour period every 8 hours.

Meropenem had no adverse effects on fertility, embryofetal development or pre and postnatal development in animals (Meropenem USPI). Vaborbactam similarly has no effect on male or female fertility in rats, on pregnancy in female rats or rabbits, on the developing embryo in rats or rabbits, and on the developing and juvenile rat when either exposed in utero, during lactation or as a juvenile.

In summary, non-clinical data support the utility and safety of vaborbactam and support the registration of meropenem-vaborbactam for the treatment of cUTI/AP.

Clinical Safety

Meropenem-vaborbactam was evaluated in an adequately controlled, randomized, double blinded, Phase 3 clinical trial for the treatment of adult patients with cUTI/AP. The overall safety database included 407 subjects treated with varying doses of mer-vab in five clinical trials: three Phase 1 trials (112 subjects), one Phase 3 pivotal trial, Study 505 (273 patients), and in an ongoing Phase 3 trial, Study 506 from which interim data for 22 patients were submitted.

Data from the non-inferiority trial (Study 505), and interim data from ongoing Study 506 (which was an open label trial studied for the indication of cUTI/AP, cIAI, HABP, VABP, and bacteremia suspected or known to be caused by carbapenem-resistant Enterobacteriaceae) served as the primary safety dataset for mer-vab safety findings. A total of 337 subjects, from both Phase 1 and Phase 3 trials were treated with the intended treatment regimen of meropenem 2 g-vaborbactam 2 g.

Overall, patient population was comparable and balanced between the two study treatment-groups in both Phase3 trials. The range of underlying comorbidities in the safety population represents that encountered in clinical practice in the U.S. population with the exception of African Americans and patients with moderate to severe renal insufficiency with CrCl<30ml/min, which were not well represented in this study.

The overall safety overview and general comparison to the comparator (piperacillin/tazobactam or Best available therapy) suggest that mer-vab has a relatively favorable safety profile. TEAEs related to study drug and discontinuation of study drug due to TEAEs were slightly higher in the comparator arms. The proportion of all TEAEs, drug related TEAEs, mild, moderate and severe TEAEs were similar in the pooled safety population. Life-threatening TEAEs were higher in the mer-vab group, whereas, severe TEAEs were higher in the comparator group. The most common TEAEs were headache, diarrhea, infusion-site phlebitis, and nausea. Headache and infusion site

inflammatory reactions were reported in a higher proportion of patients in the mer-vab group than the comparator group. The rates and frequencies of AEs were similar to what is known to occur when meropenem is used in United States for approved indications for treatment of complicated skin and skin structure infections, , complicated intra-abdominal infections , and bacterial meningitis (pediatric patients 3 months of age and older), and for cUTI (approved in Europe).

There were total of 12 deaths reported in the mer-vab development program. All deaths were reported in the Phase 3 trials, 7 (2.4%) patients in the mer-vab group and 5 (1.7%) patients in the comparator group. Four of the 12 deaths occurred in Study 505 (2 each in the mer-vab and pip-tazo group), and the majority (8) of fatalities occurred in Study 506 (5 patients in the mer-vab group and 3 patients in pip-tazo group). Of note, Study 506 enrolled patients infected with Carbapenem Resistant Enterobacteriaceae with higher degree of disease severity and high likelihood of morbidity and mortality. None of the deaths was attributed to either study drug and all events were attributed to the severity of the patients' illness, progression of disease or underlying comorbid conditions and perhaps may be lack of efficacy in some cases of death in Study 506.

Life-threatening TEAEs were only seen in the mer-vab group. These life-threatening events included: congestive cardiac failure, septic shock secondary to salpingo-oophoritis, infusion-related reaction, aspiration pneumonia, and pulmonary edema. All of these events were nonfatal, but serious AEs. Other than an infusion-related reaction, which was life-threatening and considered related to study drug (mer-vab), all other life-threatening events were assessed as unrelated to study drug but were attributed to the patients' underlying comorbidities or progression of illness and infections.

The incidence of any SAEs was similar between the mer-vab and comparator groups in Phase 3 Study 505, the Phase 3 Pool and All treated Pool. There were 11 (4.0%), and 12 (4.4%) patients in the mer-vab group and comparator group, respectively, with any SAEs in Study 505; and 20 (6.8%) and 18 (6.2%) patients in the mer-vab group and comparator group with any SAEs in the Phase 3 Pool. All SAEs occurred in Phase 3 trials except for 2 SAEs in Phase 1 trial (Study-504).

In Phase 3 trials, the most frequent SAEs (>1 patient overall), reported in both treatment groups included sepsis, septic shock, colon cancer, and pulmonary embolism. SAEs of urinary tract infection and seizures were reported for 2 subjects each in the comparator group.
Overall, frequencies of serious adverse events were similar among the two groups, (5.4% and 5.3% in mer-vab and comparator groups respectively). However, frequency of events by MedDRA System Organ Classes differed between the mer-vab and comparator arm. Serious adverse events related to cardiac disorders were reported more frequently in the mer-vab group (none was related to study drug), whereas, SAEs related to infections and infestations accounted for the majority of the SAEs in the comparator group.

In Phase 3 trials, other than an 'infusion-related reaction' which led to study drug discontinuation in 2 (0.7%) patients in the mer-vab group and 0 patients in comparator group and 'hypersensitivity' leading to discontinuations in 2 (0.7%) patients in each group, all other AEs leading to study drug discontinuation occurred in no more than 1 patient in either treatment group. The most frequently reported (>1 subject overall) AEs leading to study drug discontinuation were pyrexia, drug hypersensitivity, hypersensitivity, septic shock, and infusion related reaction (one of the two infusion-related reactions was also an SAE). Similar results were noted in the All Treated Pool.

In terms of severity of adverse events, severe TEAEs were higher in the comparator group, whereas, patients in the mer-vab group mostly developed TEAEs of mild and moderate in intensity. Severe TEAEs occurred in 12 (4.1%) of patients in the mer-vab group and 19 (6.6%) of patients in the comparator group. These accounted for 15/188 and 26/165 events in the mer-vab and comparator groups, respectively. Severe TEAEs reported for more than 1 patient included anemia (3 [1.0%] patients in each treatment group), seizure (0 patients in the mer-vab group and 2 [0.7%] patients in the comparator group), aspartate aminotransferase increased (1 [0.3%] in each treatment group), and colon cancer (1 [0.3%] in each treatment group).

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The most frequent TEAEs in the Phase 3 Pool and overall safety population were observed in the SOCs of general disorders and administration site conditions, nervous system disorders, gastrointestinal disorders and infections and infestations. Among these, apart from infections and infestations, the incidence of TEAEs in these SOCs was comparatively higher in the mer-vab group. The most frequent TEAEs in the Phase-3 Pool by preferred terms were headache, diarrhea, infusion-site phlebitis, and nausea. These were balanced between two groups except for headaches. Headache occurred at a ≥2% higher incidence in the mer-vab group than in the comparators group. No 'severe' headaches were reported and none of the headaches in either group were 'serious' or resulted in discontinuation of study drug or discontinuation from the study. TEAEs of headache and infusion related reactions were disproportionately higher in the mer-vab group as compared to comparator in both Phase 3 Pool and All Treated Pool.

TEAEs of special interest were selected based on the known safety profile of meropenem and included seizures, pseudomembranous colitis/CDAD, and hypersensitivity reactions. No seizures were reported with meropenem-vaborbactam and the incidences of the other TEAEs of special interest were comparable across the treatment groups.
In the Phase 3 Pool, 4 (2.4%) patients in the mer-vab group and 5 (1.7%) patients in comparator group developed hypersensitivity reactions. In the All Treated Pool, 11 (2.7%) patients in the mer-vab and 7 (2.1%) patients in comparator group had an AE related to hypersensitivity. The hypersensitivity reactions led to discontinuation of study medication in 2 patients in the mer-vab group and 3 patients in the comparator group.

In the Phase 3 Pool, a similar proportion of patients had a study drug-related TEAE (15.9% and 15.2% in the mer-vab and compactor groups, respectively). The proportion of subjects with drug-related headache and infusion-site phlebitis was higher in the mer-vab group (headache: 4.4%; infusion site phlebitis: 2.0%) than in comparator group (1.0% and 0.7%, respectively). Similarly in the Overall Safety Pool, proportion of subjects with a TEAE assessed as related to study drug was consistent across the treatment groups (21.6% and 21.9%, respectively).

There were no clinically relevant differences between mer-vab and comparators for clinical laboratory parameters. There was no evidence of drug-induced liver injury or renal toxicity with meropenem-vaborbactam. Laboratory abnormalities characterized as severe included alanine aminotransferase increase (1 in the comparator group), aspartate amino transferase increased (1 in each treatment group), , blood creatine phosphokinase increased (1 in the comparator group) , blood creatinine increased (1 in the comparator group), hypoglycemia and hypokalemia (1 each in the mer-vab group), and fibrin-D dimer increased (1 in the comparator group).

There were no clinically relevant differences in vital signs between mer-vab and comparators. Overall, ECG data from Phase 1 and 3 studies with meropenem, vaborbactam, and the combination of the two, do not suggest that either drug has a clinically significant effect on ECG parameters, including the QTc interval.

The regulatory decision on this NDA is directly related to the risk-benefit ratio. Meropenem-vaborbactam is non-inferior to piperacillin/tazobactam for treatment of cUTI/AP at both primary and secondary endpoints. From the analysis of the safety database for the cUTI/AP indications, mer-vab appears to have a similar safety profile to that of the active comparators and to that described for the carbapenem class of antibacterial drugs. However, to detect rare but potentially serious adverse events in target population in clinical setting, a continued pharmacovigilance would be required. Assessment of safety of mer-vab in African Americans and patients with creatinine clearance <30 ml/min is limited in this NDA.

Overall, mer-vab for the treatment of cUTI/AP appears to have a favorable safety profile and findings from this review supports that risk does not outweigh the potential benefit of use of mer-vab for treatment of patients with complicated urinary tract infections.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting is not planned for this NDA.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are ongoing. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted.

10.2. Patient Labeling

Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, patient labeling was not yet updated.

10.3. Nonprescription Labeling

Not applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

No identified safety issues warrant consideration of REMS.

11.1. Recommendations on REMS

The Division of Risk Management in the Office of Medication Error Prevention and Management reviewed the application and determined that a Postmarket Risk and Evaluation Strategy (REMS) for the management of the risks associated with meropenem-vaborbactam were not recommended. This reviewer agrees that there is adequate safety information to recommend routine pharmacovigilance as a sufficient strategy for postmarket risk evaluation.

12 Post marketing Requirements and Commitments

This section will be updated as the review process and discussions continue.

The following Post-marketing Requirements are planned for this application:

1. Pediatric Research and Equity Act (PREA) requirements:

Pediatric Study Plan was agreed between the agency and the Applicant on December 2, 2015 with concurrence from the Pediatric Review Committee.
The Applicant will conduct following three clinical trials in children birth to less than 18 years of age to support the use of meropenem-vaborbactam in the indications of cUTI or AP in pediatric patients:

Study 507: A Phase 1, open-label, dose-finding, single-dose, PK, safety, and tolerability study of meropenem/RPX7009 in pediatric subjects (birth to < 18 years) with (b) (4) bacterial infections (b) (4)

(b) (4) A Phase 2, randomized, single-blind, active comparator study to evaluate the safety, tolerability, and PK of meropenem/RPX7009 versus piperacillin/tazobactam for the treatment of pediatric subjects from 3 months to < 18 years of age with cUTI (including AP).

(b) (4) A Phase 2, open-label, active comparator study to evaluate the safety, tolerability, and PK of multiple dose infusions of meropenem/RPX7009 versus comparator in neonates (≤ 90 days of age) with late-onset sepsis, (b) (4)

Potential recommendations for Post-marketing requirements are as follows:

- *i) Surveillance for developing resistance to meropenem-vaborbactam over a five-year period*
- *ii) Conduct a TQT study for this product as a PMR to exclude small QT prolongation effects (10 msec threshold).*
- *iii) This reviewer also suggests assessment of patients with moderate to severe renal insufficiency either as PMR or surveillance during post marketing period.*

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13 Appendices

13.1. References

References have been placed as footnotes where needed throughout this review.

13.2. Financial Disclosure

There were no financial disclosures to report individually or collectively.
This NDA includes covered clinical studies Rempex-402, Rempex-501, Rempex-503, Rempex-504, Rempex-505, and Rempex-506, with the signed Form FDA 3454, with an attachment listing those clinical investigators who do not have financial information to disclose. There were no investigators who had a financial arrangement to report.

13.3. PK Studies

Table 100 Trials Involving the Examination of the PK Properties of Meropenem and/or Vaborbactam

Study Number	Phase	Study Design	Dosing	PK Sampling Scheme(s)
Study 402	1	Phase I, randomized, double-blind, placebo-controlled, ascending single- and multiple-dose study evaluating safety, tolerability and PK in healthy adult subjects	Vaborbactam-single and multiple (q8h for 8 to 10 days); 250 – 2000 mg as 3-h infusion	Intensive blood sampling on Days 1 and 8/10; urine collected over 48 hours
Study 501	1	Phase I, randomized, double-blind, placebo controlled, SAD and MAD study in healthy adult subjects	Single and multiple doses of meropenem and vaborbactam alone or in combination	Intensive blood sampling on multiple days; urine collected over 48 hours on multiple days
Study 503	1	Phase I, single-center, randomized, open-label study evaluating the plasma, epithelial lining fluid and alveolar macrophage concentrations in healthy adult subjects	Meropenem 2g – vaborbactam 2g over 3-h q8h (3 doses)	Intensive blood sampling; BAL performed based upon randomized schedule
Study 504	1	Phase I, multicenter, open-label, single-dose study evaluating the PK and safety of meropenem and vaborbactam in subjects with varying degrees of renal impairment	Meropenem 1 g-vaborbactam 1 g over 3-h (1 dose)	Intensive blood sampling over 24 hours after the dose; urine collected over 72 hours
Study 505	3	Phase 3, multicenter, randomized (1:1), parallel- group, double-blind, double dummy study	Meropenem 2 g-vaborbactam 2 g over 3-h q8h for at least 15 doses and up to 10 days (14 days in subjects with bacteremia)	Day 1 at 0.5 and 2-3 h after the end of the first infusion; Day 3 within 0.5 h of end of infusion
Study 506	3	Phase 3, multicenter, randomized (2:1), open-label study of Meropenem-vaborbactam versus best available therapy in subjects with serious infections due to known or suspected CRE	Meropenem 2 g-vaborbactam 2 g over 3-h q8h for 7-14 days	Day 1 at 0.5 and 2-3 h after the end of the first infusion; Days 3 and 5 within 0.5 h of end of infusion
Source: Module 2.7.2 Summary of Clinical Pharmacology Studies				

13.4. Patient Disposition- Study 505 [MITT and m-MITT Population]

Table 101 Disposition of patients (MITT and m-MITT Population)

	MITT		m-MITT	
	mer-vab (n=272) n (%)	**pip-tazo (n=273) n (%)**	**mer-vab (n=192) n (%)**	**pip-tazo (n=182) n (%)**
Patients who completed study treatment	249 (91.5)	235 (86.1)	182 (94.8)	161 (88.5)
Patients who did not complete study drug treatment	23 (8.5)	38 (13.9)	10 (5.2)	21 (11.5)
Reasons for not completing study drug treatment				
Physician decision	8 (2.9)	13 (4.8)	4(2.1)	9(4.9)
Withdrawal by subject	7 (2.6)	4 (1.5)	3 (1.6)	2 (1.0)
Adverse event	6 (2.2)	14 (5.1)	3(1.6)	8(4.4)
Lack of Efficacy	0 (0.0)	3 (1.1)	0 (0.0)	1 (0.5)
Other	2 (0.7)	3 (1.1)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	3 (1.1)	0 (0.0)	1(0.5)
Subjects who did not complete IV study treatment	22 (8.1)	35 (12.8)	10 (5.2)	19 (10.4)
Subjects who started oral step-down study treatment	156 (57.4)	144 (52.7)	117 (60.9)	94 (51.6)
Subjects who were started on oral step-down but did not complete the oral treatment	1 (0.6)	3 (2.1)	0 (0.0)	2 (2.1)
Subjects who completed the study	258 (94.9)	250 (91.6)	183 (95.3)	169 (92.9)
Subjects who did not complete the study	14 (5.1)	23 (8.4)	9 (4.7)	13 (7.1)
Reasons for not completing the Study				
Lost to follow-up	**5 (1.8)**	**10 (3.7)**	5 (2.6)	6 (3.3)
Withdrawal by subject	5 (1.8)	7 (2.6)	2 (1.0)	3 (1.6)
Adverse event	3 (1.1)	3 (1.1)	2 (1.0)	3 (1.6)
Physician decision	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	3 (1.1)	0 (0.0)	1 (0.5)
Source: CLINICAL REVIEWERS' ANALYSIS				

13.5. Individual Reasons for Premature Discontinuations Due to Adverse Events by Treatment Group

Table 102 ***Premature Discontinuations of study treatment due to AEs (mer-vab group) – Study 505***

No	*Subject ID IFN Type /age /sex /region*	*AE Start /End Day*	*CCI*	*CrCL*	*AE PT*	*Severity/Relatedness/Outcome*	*Clinical Reviewer's Comments*
1	*505-300-001-527 AP/88/F/W/Eu*	*8/8*	*6*	*>=30 - 50*	*Pyrexia*	*Mild/Rel /Resolved*	*[Infusion related Fever]*
2	*505-604-004-502 AP/67/M/Other/ Rest of World*	*1/1*	*3*	*>50*	*Infusion related reaction*	*Severe/Rel /Recovered*	
3	*505-703-001-502 AP/76/F/W/Eu*	*11/11 10/10*	*6*	*>50*	*Hypersensitivity*	*Mild/Unlikely Rel /Resolved*	*Probably Related: (edema of tongue and lips with paresthesia on D-10 while receiving last dose. Last dose withheld)-Patient was treated with hydrocortisone*
4	*505-703-005-512 AP/46/F/W/Eu*	*6/14*	*2*	*>50*	*Drug hypersensitivity*	*Mild/Not –Rel /Resolved*	*Pt completed 5 D of infusion. had H/O allergy to Levofloxacin NOT RELATED*
5	*505-804-001-507 cUTI/61/F/W/Eu*	*3/3*	*6*	*>50*	*Infusion related allergic reaction*	*Severe/Rel/Resolved*	
6	*505-804-008-506 AP/24/F/W/Eu*	*4/4 (9th infusion)*	*0*	*>50*	*Tremor [HA, Gen Body tremor during 9th infusion]*	*Mod/Rel/Resolved*	
7	*505-703-005-510 cUTI/42/F/W/Eu*	*2/6*	*1*	*>50*	*-Septic shock -Salpingo-oophoritis*	*Severe/NOT Rel /Recovered*	

Discontinuation of Treatment due to AEs (Pip-tazo group)- Study 505

No.	**SUBJ-ID/ IFN Type**	**AE PT term**	**Tx Start Day/ AE day**	**Tx End Day/ AE day**	**Severity /REL**	**Outcome**	**Comments**
1	*505-100-006-504/ AP*	*Angina Pectoris, HTN Crisis*	*11/11 11/14*	*11/14 11/14*	*Mod Poss. Rel*	*EOIVT on day 4: Success (P mirabilis Cure) TOC on day 10: Success (P. Mirabilis)*	*Received 4 days of IV Tx*

2	505-100-008-504/ AP	Blood Bilirubin Increased	3/18 3/21	3/21 3/28	Mild/ Not Rel	EOIVT on day 4: Cure TOC: Failure	Received 4 days of IV Tx
	505-112-004-505*/ AP	Pseudomembranous Enterocolitis	10/21 10/26	10/23 10/26	Mod/ Poss. Rel	EOIVT day4 : Failure	Received 3 days of IV Tx
3	505-158-001-508/ AP	Pyrexia, (1/23) Rash (1/26)	1/20 1/23 (pyrexia) 1/26 (rash)	1/25 1/25 (pyrexia) 1/28 (rash)	Mod/ Poss. Rel	EOIVT: Failure TOC: failure	Received 6 days of IV Tx
4	505-300-001-514/ AP	Septic Shock	12/6 12/6	12/7 12/7	Severe/ Not Rel	EOIVT: Failure TOC: failure (E Coli)	Received 3 days of IV Tx FATAL
5	505-300-001-520/ AP	Vomiting	12/31 1/6	1/7 1/7	Mild/ Not Rel	EOIVT: Cure TOC: Cure (K. Pneumoniae)	Received 6 days of IV Tx and 3 days of Oral Tx
6	505-300-001-530/AP	Dyspnea	¾ 3/7	3/7 3/8	Mild/ Poss. Rel	EOIVT and TOC: Failure	Received 4 days of IV Tx
7	505-642-003-501/ cUTI	Hypersensitivity	11/23 11/24	11/24 11/24	Mod/ Prob Rel	EOIVT and TOC: Failure (E. Coli)	Received 2 days of IV Tx
8	505-703-005-509/ AP	Pulmonary Embolism	8/27 8/29	8/29 8/29	Severe/ Not Rel	EOIVT and TOC: Indeter (E. Coli)	Received 3 days of IV Tx FATAL
9	505-703-005-511/ AP	Hypersensitivity (allergy to Levofloxacin)	11/4 11/10	11/11 11/13	Mild/ Not Rel	EOIVT : Clin Outcome-Improveme; TOC: Not assessed	Received 15 doses (6 days) of IV Tx and 3 days of Oral Tx
10	505-724-009-506/ AP	CVA	¾ 3/5	3/5 3/21	Severe/ Not Rel	EOIVT: indeterminate TOC: indeterminate	Received 2 days of IV Tx
11	505-804-005-527/ AP	Blood Creatinine Increased	10/30 12/3	12/3 12/8	Severe/ Not Rel	EOIVT Clin Out : Failure TOC Clin Out: failure	Received 9 doses (4 days) of IV Tx
12	505-804-007-504/ cUTI	Post-Operative Wound Infection	7/20 7/28	7/29 8/6	Mod/ Not Rel	EOIVT: Clin Out-Indeterminate; TOC: Clin Out Failure	Received 27 doses (10 days) of IV Tx
13	505-804-008-505/ AP	Colon Cancer	9/3 9/7	9/8 10/3	Severe/ Not Rel	EOIVT on Day 5 *** (E. Faecalis)	Received 15 doses (6 days) of IV Tx

Source: Clinical Reviewers' Analysis; e CFR

13.6. Table of Subjects with Key Protocol Violations

Table 103 Key Protocol Inclusion/Exclusion Violations (Study-505) - MITT (Safety) Population

#	Patient Number	Deviation Type	Description/Comments	mMITT
Meropenem-Vaborbactam				
1	642-001-501	Inclusion Criteria	Subject does not have documented or suspected cUTI or AP	Yes
2	642-001-508	Inclusion Criteria	Subject does not have documented or suspected cUTI or AP	Yes
3	703-005-508	Exclusion Criteria	Subject received more than one short acting antibiotic agent within 48 hours prior to randomization	Yes
4	703-005-512	Exclusion Criteria	Subject received more than one short acting antibiotic agent within 48 hours prior to randomization.	Yes
5	705-002-502	Exclusion criteria	Subject has known non-renal source of infection Patient Continued in Study Criteria (pneumonia) within 7 days of randomization.	No
		Inclusion Criteria	Subject does not have documented or suspected cUTI or AP.	
		Restricted Concomitant Medication	The patient received another Gram negative antibiotic for a reason other than treatment failure.	
6	804-005-532	Exclusion criteria	Subject received more than one short acting antibiotic agent within 48 hours prior to randomization	No
7	804-005-545	Exclusion criteria	Subject received more than one short acting antibiotic agent within 48 hours prior to randomization	Yes
8	804-009-503	Exclusion criteria	Presence of Exclusion criteria#17: Receipt of any potentially therapeutic antibiotic agent within 48 hours before randomization	Yes
		Exclusion criteria	Subject received more than one short acting antibiotic agent within 48 hours prior to randomization	
9	804-009-527	Exclusion criteria	Presence of Exclusion criteria#17: Receipt of any potentially therapeutic antibiotic agent within 48 hours before randomization	Yes
		Exclusion criteria	Subject received more than one short	

			acting antibiotic agent within 48 hours prior to randomization	
	Piperacillin-tazobactam			
1	804-005-538	Exclusion criteria	Subject required at time of enrollment additional systemic antibiotic therapy (1 dose of ciprofloxacin within 48 hours before randomization).	Yes

Source: Clinical Reviewer's analysis; Listing 17.7.2.2
Note: Each of above listed patients may have had additional protocol violations related to study drug administration, SAE reporting or other procedures which are not listed here.

13.7. Table of Demographic Characteristics (Primary Efficacy and Safety Population)- Study 505

Table 104 Demographics by Subgroup (mMITT and MITT Population) - Study 505

	Study Groups mMITT			Study Groups MITT		
Demographic Parameters	M/V N=192	P/T N=182	All N=374	M/V N=272	P/T N=273	All N=545
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age						
< 65 years	130 (68)	105 (58)	235 (63)	185 (68)	170 (62)	355 (65)
>= 75 years	27 (14)	38 (21)	65 (17)	39 (14)	46 (17)	85 (16)
65- < 75 years	35 (18)	39 (21)	74 (20)	48 (18)	57 (21)	105 (19)
Sex						
F	125 (65)	120 (66)	245 (65)	181 (66.5)	180 (66)	361 (66)
M	67 (35)	62 (34)	129 (35)	91 (33.5)	93 (34)	184 (34)
Race						
White	178 (93)	169 (93)	347 (93)	254 (93)	252 (92)	506 (93)
Other	7 (4)	8 (4)	15 (4)	10 (4)	12 (4)	22 (4)
Asian	4 (2)	3 (2)	7 (2)	5 (2)	5 (2)	10 (2)
Black or African American	3 (1.5)	2 (1)	5 (1)	3 (1)	4(1)	7 (1)
Ethnicity						
Hispanic or Latino	14 (7)	12 (7)	26 (7)	24 (9)	19 (7)	43 (8)
Not Hispanic or Latino	178 (93)	170 (93)	348 (93)	248 (91)	254 (93)	502 (92)
Region						
Europe	173 (90)	163 (89)	336 (90)	244 (90)	243 (89)	487 (89)
Rest of World	12 (6)	10 (5)	22 (6)	16 (6)	16 (6)	32 (6)
North America	3 (2)	6 (3)	9 (2)	8 (3)	9 (3)	17 (3)
Asia Pacific	4 (2)	3 (2)	7 (2)	4 (1.5)	5 (2)	9 (2)
Infection Type						
Acute Pyelonephritis	120 (62)	101 (55)	221 (59)	161 (59)	161 (59)	322 (59)
cUTI with Non-Removable Source of Infection	37 (19)	43 (24)	80 (21)	53 (19.5)	51 (19)	104 (19)
cUTI with Removable Source of Infection	35 (18)	38 (21)	73 (19)	58 (21)	61 (22)	119 (22)

13.6 Table- Baseline Disease Characteristics by Subgroup

Table 105 Baseline Disease Characteristics by Subgroup (m-MITT and MITT Population)-Study 505

	Study Groups (m-MITT/Efficacy Population)			Study Groups (MITT/Safety Population)		
	M/V N-192	P/T N=182	All N=374	M/V N-272	P/T N=273	All N=545
Categories	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
CrCL-group						
Missing	2 (1)	3 (2)	5 (1)	4 (1.5)	3 (1)	7 (1)
<30 mL/min	1 (0.5)	1 (0.5)	2 (0.5)	2 (1)	2 (1)	4 (1)
>50 mL/min	169 (88)	156 (86)	325 (87)	237 (87)	233 (85)	470 (86)
30 - 50 mL/min	20 (10)	22 (12)	42 (11)			
Diabetes Status						
N	160 (83)	148 (81)	308 (82)	230 (85)	229 (84)	459 (84)
Y	32 (17)	34 (19)	66 (18)	42 (15)	44 (16)	86 (16)
Presence of SIRS						
N	137 (71)	121 (66)	258 (69)	195 (72)	183 (67)	378 (69)
Y	55 (29)	61 (33)	116 (31)	77 (28)	90 (33)	167 (31)
Charlson Score						
<=2	89 (46)	77 (42)	166 (44)	129 (47)	126 (46)	255 (47)
>=3	103 (54)	105 (58)	208 (56)	143 (53)	147 (54)	290 (53)
Bacteremia at baseline						
N	175 (91)	164 (90)	339 (91)	241 (89)	243 (89)	484 (89)
Missing	5 (3)	3 (2)	8 (2)	19 (7)	15 (5.5)	34 (6)
Y	12 (6)	15 (8)	27 (7)	12 (4)	15 (5)	27 (5)
Prior short-acting antibiotic use, single-dose						
N	186 (97)	176 (97)	362 (97)	260 (96)	264 (97)	525 (96)
Y	6 (3)	6 (3)	12 (3)	12 (4)	9 (3)	21 (4)
Source: Clinical Reviewers' Analysis						

13.7 Baseline Clinical Characteristics of (MITT and m-MITT Population)-Study 505

	Treatment Groups			
	MITT		m-MITT	
Characteristics	**M-V** (N= 272)	**P/T** (N= 273)	**M/V** N=192	**P/T** N=182
	n (%)	**n (%)**	**n (%)**	**n (%)**
Infection Type				
Acute Pyelonephritis	161/272 (59.2)	161/273 (59.0)	120 (62)	101 (55)
cUTI with Non-Removable Source of Infection	58/272 (21.3)	61/273 (22.3)	37 (19)	43 (24)
cUTI with Removable Source of Infection	53/272 (19.5)	51/273 (18.7)	35 (18)	38 (21)

Signs/Symptoms experienced by Patient				
Pyuria	271/272 (99.6)	273/273 (100.0)	192 (100)	182 (100)
Dysuria	194/272 (71.3)	185/273 (67.8)	143 (74)	124 (68)
C-T Angle tenderness	192/272 (70.6)	185/273 (67.8)	138 (72)	115 (63)
Flank Pain	186/272 (68.4)	194/273 (71.1)	132 (69)	121 (66)
Supra-pubic pain/discomfort	170/272 (62.5)	159/273 (58.2)	125 (65)	106 (58)
Urinary frequency	177/272 (65.1)	172/273 (63.0)	124 (65)	112 (61)
Fever	157/272 (57.7)	171/273 (62.6)	115 (60)	115 (63)
Urinary Urgency	142/272 (52.2)	147/273 (53.8)	102 (53)	102 (56)
Abdominal Pain	90/272 (33.1)	93/273 (34.1)	56 (29)	62 (34)
Nausea	114/272 (41.9)	105/273 (38.5)	76 (40)	66 (36)
Vomiting	27/272 (9.9)	18/273 (6.6)	20 (10)	12 (7)
Mean Temperature (°C) within 24 hours prior to enrollment	38.7	38.7	38.6	38.7
Source: CLINICAL REVIEWERS' ANALYSIS and CSR, Table 16; CT : costo-vertebral				

13.8. Table of Charlson Comorbidity Index Scores for Study 505 and 506

Table 106 Table of Charlson Comorbidity Index Scores for Study 505 and 506

Study 505						Study 506			
	Mer-vab (N=273)		Pip-Taz (N=272)			Mer-vab (N=23)		BAT (N=16)	
CCI Score	n	%	n	%	CCI Score	n	%	n	%
0	70	25.74	82	30.15	0	0	0.00	1	4.35
1	22	8.09	22	8.09	1	0	0.00	1	4.35
2	37	13.60	22	8.09	2	0	0.00	1	4.35
3	48	17.65	40	14.71	3	2	12.50	0	0.00
4	32	11.76	32	11.76	4	1	6.25	2	8.70
5	31	11.40	30	11.03	5	4	25.00	7	30.43
6	16	5.88	24	8.82	6	2	12.50	2	8.70
7	5	1.84	8	2.94	7	2	12.50	3	13.04
8	7	2.57	7	2.57	8	1	6.25	0	0.00
9	1	0.37	5	1.84	9	2	12.50	4	17.39
10	3	1.09	1	0.37	10	0	0.00	1	4.35
Source: IR request to the Applicant ; Clinical Reviewers' Analysis									

Source: Clinical Reviewers' Analysis

13.9. Summary of outcomes Study 505 subjects from Sites 703-005 and 616-002 with major protocol violations

Table 107 Summary of Study 505 subjects at Sites 703-005 and 616-002

Subject ID	Treatment group	Acute pyelonephritis	m-MITT population	Overall Response at EOIV	Overall Response at TOC	Clinical Outcome at TOC
616-003-501	M/V	N	N	N/A	N/A	Cure
616-003-504	P/T	N	Y	Success	Success	Cure
616-003-505	M/V	N	N	N/A	N/A	Cure
616-003-506	P/T	N	Y	Success	Failure	Cure
616-003-507	M/V	Y	Y	Success	Success	Cure
616-003-508	M/V	N	N	N/A	N/A	Cure
703-005-501	P/T	N	Y	Success	Indeterminate	Not Assessed
703-005-502	P/T	N	Y	Success	Failure	Cure
703-005-503	P/T	N	N	N/A	N/A	Cure
703-005-504	M/V	Y	Y	Success	Success	Cure
703-005-505	M/V	N	Y	Success	Success	Cure
703-005-506	P/T	Y	Y	Success	Indeterminate	Indeterminate
703-005-507	M/V	N	Y	Success	Failure	Cure
703-005-508	M/V	Y	Y	Success	Success	Cure
703-005-509	P/T	Y	Y	Indeterminate	Indeterminate	Not Assessed
703-005-510	M/V	N	N	N/A	N/A	Not Assessed
703-005-511	P/T	Y	N	N/A	N/A	Not Assessed
703-005-512	M/V	Y	Y	Success	Success	Cure
703-005-513	P/T	N	Y	Success	Success	Cure

Note: The study site is identified by the first 6 numbers of the subject ID. M/V=meropenem/vaborbactam, P/T=piperacillin/tazobactam, Y=Yes, N=No.
Note: Due to the relatively small number of subjects from the affected study sites and the insensitivity of the main trial conclusions to these subjects, the other analyses in this review do not attempt to exclude these study sites.

13.10. Ad Hoc Table for Summary of Microbiological Eradication Rate by Baseline Pathogen and MIC Breakpoints Based on FDA CFU/ml Criteria (m-MITT Population-Study 505)

Table 108 Summary of Microbiological Eradication Rate by Baseline Pathogen and MIC Breakpoints Based on FDA CFU/ml Criteria (m-MITT)-505 [Ad Hoc Table]

Time point/ Antimicrobial	FDA Breakpoint (mcg/ml)	Mer-vab N=192	Pip-tazo N=182
Enterobacter cloacae species complex			
EOIVT			
Meropenem	Susceptible (<=1)	9/9	4/4
Piperacillin-Tazobactam	Susceptible (<=16)	5/5	1/1
	Intermediate (32-64)	0/0	1/1
	Resistant (>64)	4/4	**2/2**
	Overall Success by ESBL (+)	7/7	3/3
	Overall Success by ESBL (-)	2/2	1/1
TOC			
Meropenem	Susceptible (<=1)	7/9	2/4
Piperacillin-Tazobactam	Susceptible (<=16)	4/5	0/1
	Intermediate (32-64)	0/0	1/1
	Resistant (>64)	3/4	**1/2**
	Overall Success by ESBL (+)	**5/7**	3/3
	Overall Success by ESBL (-)	2/2	0/1
Escherichia coli			
EOIVT			
Meropenem	Susceptible (<=1)	118/120 (98%)	103/113 (91%)
	Intermediate (=2)	1/1	0/0
Piperacillin-Tazobactam	Susceptible (<=16)	104/106 (98%)	92/99 (93%)
	Intermediate (32-64)	11/11 (100%)	6/9 (67%)
	Resistant (>64)	7/7 (100%)	6/6 (100%)
	Overall Success by ESBL (+)	27/27	25/27 (93%)
	Overall Success by ESBL (-)	92/94 (98%)	82/87 (94%)
TOC			
Meropenem	Susceptible (<=1)	87/120 (72%)	70/113 (62%)
	Intermediate (=2)	1/1 (100%)	0/0
Piperacillin-Tazobactam	Susceptible (<=16)	78/106 (74%)	62/99 (63%)
	Intermediate (32-64)	7/11 (64%)	4/9 (45%)
	Resistant (>64)	4/7 (57%)	4/6 (67%)
	Overall Success by ESBL (+)	**19/27 (70%)**	16/27 (60%)
	Overall Success by ESBL (-)	77/94 (82%)	66/87 (76%)
Klebsiella pneumoniae			
EOIVT			
Meropenem	Susceptible (<=1)	26/27 (96%)	23/25 (92%)
	Intermediate (=2)	1/1	0/0
	Resistant (>=4)	1/1	1/1
Piperacillin-Tazobactam	Susceptible (<=16)	14/15 (93%)	14/15 (93%)
	Intermediate (32-64)	0/0	3/3

Time point/ Antimicrobial	FDA Breakpoint (mcg/ml)	Mer-vab N=192	Pip-tazo N=182
	Resistant (>64)	14/14	7/8 (88%)
Overall Success by ESBL (+)		20/21 (95%)	15/15 (100%)
Overall Success by ESBL (-)		8/8 (100%)	10/11 (91%)
TOC			
Meropenem	Susceptible (<=1)	16/27 (59%)	13/25 (52%)
	Intermediate (=2)	1/1	0/0
	Resistant (>=4)	1/1	0/1
Piperacillin-Tazobactam	Susceptible (<=16)	9/15 (60%)	9/15 (60%)
	Intermediate (32-64)	0/0	1/3 (33%)
	Resistant (>64)	9/14 (64%)	3/8 (38%)
	Overall Success by ESBL (+)	**12/21 (57%)**	6/15 (40%)
	Overall Success by ESBL (-)	5/8 (62%)	7/11 (64%)
Proteus Mirabilis			
EOIVT			
Meropenem	Susceptible (<=1)	6/6	12/12
Piperacillin-Tazobactam	Susceptible (<=16)	6/6	11/11
	Intermediate (32-64)	0/0	1/1
Overall Success by ESBL (+)		4/4	2/2
Overall Success by ESBL (-)		2/2	10/10
TOC			
Meropenem	Susceptible (<=1)	3/6 (50%)	7/12 (58%)
Piperacillin-Tazobactam	Susceptible (<=16)	3/6 (50%)	6/11 (55%)
	Intermediate (32-64)	0/0	1/1
	Overall Success by ESBL (+)	3/4 (75%)	2/2
	Overall Success by ESBL (-)	0/2	7/10 (70%)
Pseudomonas aeruginosa			
EOIVT			
Meropenem	Susceptible (<=1)	2/2	6/6
	Resistant (>=8)	2/2	2/4 (50%)
Piperacillin-Tazobactam	Susceptible (<=16)	2/2	4/4
	Intermediate (32-64)	1/1	1/2 (50%)
	Resistant (>64)	1/1	3/4 (75%)
	Overall Success by ESBL (+)	2/2	6/8 (75%)
	Overall Success by ESBL (-)	2/2	2/2
TOC			
Meropenem	Susceptible (<=1)	2/2	3/6 (50%)
	Resistant (>=8)	2/2	1/4 (25%)
Piperacillin-Tazobactam	Susceptible (<=16)	2/2	2/4 (50%)
	Intermediate (32-64)	1/1	0/2
	Resistant (>64)	1/1	2/4 (50%)
	Overall Success by ESBL (+)	2/2	3/8 (38%)
	Overall Success by ESBL (-)	2/2	1/ 2 (50%)
Enterococcus faecalis			
EOIVT	ESBL (-)	12/12	13/14

Time point/ Antimicrobial	FDA Breakpoint (mcg/ml)	Mer-vab N=192	Pip-tazo N=182
TOC	ESBL (-)	7/ 12 (58%)	11/14 (79%)
Source: Ad Hoc Table, CAS and Clinical Reviewers' Analysis			

13.11. TEAEs by Preferred Terms in patients with creatinine clearance <30 ml/min (All Treated Pool)

Table 109 TEAEs by Preferred Terms in patients with CrCL <30 ml/min (All Treated Pool)

					Tx Group	
USUBJID	GROUP	MedDRA PT	SEV	*AREL*	Mer-vab	Comp
504-04-640	GROUP 5 (ESRD)	Skin injury	MILD	*Not Related*	1	
504-05-612	GROUP 3 (SEVERE RI)	Diarrhea	MILD	*Possibly Related*	1	
504-05-614	GROUP 2 (MOD RI)	Constipation	MILD	*Not Related*	1	
		Headache	MILD	*Possibly Related*	1	
504-05-633	GROUP 5 (ESRD)	Paresthesia	MILD	*Not Related*	1	
		Vomiting	MILD	*Not Related*	1	
504-05-634	GROUP 5 (ESRD)	Abdominal pain	MILD	*Unlikely Related*	1	
		Diarrhea hemorrhagic (SAE)	SEVERE	*Possibly Related*	1	
504-05-637	GROUP 5 (ESRD)	Muscle spasms	MILD	*Not Related*	1	
		Prostate cancer metastatic (SAE)	SEVERE	*Not Related*	1	
504-05-642	GROUP 5 (ESRD)	Headache	MILD	*Possibly Related*	2	
505-804-005-527	AP	Blood creatinine increased	SEVERE	*Not Applicable*		1
505-804-009-524	cUTI -NRS	Azotemia (SAE)	SEVERE	*Not Related*	1	
		Hematuria	MOD	*Not Related*	1	
		Oliguria	SEVERE	*Not Related*	1	
		Ureteric obstruction	SEVERE	*Not Related*	1	
506-300-001-605	AP	Anemia	SEVERE	*Not Related*	1	
		Blood magnesium decreased	MILD	*Not Related*	1	
506-300-001-610	AP	Sepsis (SAE)	SEVERE	*Not Related*	1	
506-300-001-613	cUTI	Pulmonary edema (SAE)	SEVERE	*Not Related*	2	
		Rash	MILD	*Possibly Related*	1	
506-840-010-603	BACTEREMIA	Asthenia	MILD	*Not Related*		1

					Tx Group	
USUBJID	GROUP	MedDRA PT	SEV	*AREL*	Mer-vab	Comp
		Diarrhea	MILD	*Unlikely Related*		1
		edema peripheral	MILD	*Not Related*		2
		Pneumothorax	SEVERE	*Not Related*		1
		Renal impairment	SEVERE	*Not Related*		1
		Thrombocytopenia	MILD	*Possibly Related*		1
		Tremor	MILD	*Not Related*		1

Source: Clinical Reviewers' Analysis
CrCL= creatinine clearance; ERSD= End stage renal disease

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/s/

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06/08/2017

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