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ARTICLE

Population pharmacokinetic/pharmacodynamic assessment of imipenem/cilastatin/relebactam in patients with hospital-acquired/ventilator-associated bacterial pneumonia

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Abstract

In the phase III RESTORE-IMI 2 study (ClinicalTrials.gov: NCT02493764), the combination antibacterial agent imipenem/cilastatin/relebactam (IMI/REL) demonstrated noninferiority to piperacillin/tazobactam for the end points of all-cause mortality at day 28 and favorable clinical response at the early follow-up visit in adult participants with gram-negative hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP). Existing population pharmacokinetic models for imipenem (IPM) and REL were updated using data from patients with HABP/VABP from RESTORE-IMI 2. Creatinine clearance (CrCl), body weight, infection type, and ventilation status were significant covariates in the updated model. The following simulations were performed to calculate the pharmacokinetic/pharmacodynamic joint probability of target attainment among patients with HABP/VABP and varying degrees of renal function: augmented renal clearance (CrCl ≥150 ml/min), normal renal function (CrCl ≥90 to <150 ml/min), renal impairment (mild, CrCl ≥60 to <90 ml/min; moderate, CrCl ≥30 to <60 ml/min; or severe, CrCl ≥15 to <30 ml/min), and end-stage renal disease (CrCl <15 ml/min). At the recommended IMI/REL dosing regimens across renal categories, greater than 90% of patients in all renal function groups were predicted to achieve joint pharmacokinetic/pharmacodynamic targets at a minimum inhibitory concentration breakpoint of ≤2 μg/ml, regardless of ventilation status. This modeling and simulation analysis supports use of the recommended IMI/REL dosing regimens, adjusted based on renal function, in patients with HABP/VABP.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Imipenem (IPM)/cilastatin/relebactam (REL) is approved for the treatment of patients with hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP), a critically ill population likely to present with pathophysiological changes that can affect pharmacokinetic parameters of antibacterials. Existing population pharmacokinetic models for IPM and REL were developed with limited data from participants with HABP/VABP.

WHAT QUESTION DID THIS STUDY ADDRESS?

This analysis integrated data from the phase III RESTORE-IMI 2 study into an existing population pharmacokinetic model to evaluate the effects of covariates on IPM and REL exposures and to analyze pharmacokinetic/pharmacodynamic probability of target attainment (PTA) in patients with HABP/VABP.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Patients with HABP/VABP had slightly higher exposures than healthy participants and patients with complicated urinary tract or intra-abdominal infection. High, adequate joint PTA was attained regardless of ventilation status. These findings were consistent among patients with impaired renal function.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

These findings confirm that the 500/500/250-mg IPM/cilastatin/REL dose, adjusted for renal function, is appropriate for patients with HABP/VABP.

INTRODUCTION

Hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) are common nosocomial infections that are associated with a 10%–40% mortality rate.[1–4] HABP/VABP is commonly caused by multidrug-resistant gram-negative bacteria; these patients face an approximately three-fold increased risk of death.[5–7] Novel antibacterial therapies are needed to effectively target drug-resistant isolates.

Relebactam (REL) is a small-molecule β-lactamase inhibitor with activity against class A β-lactamases (e.g., extended-spectrum β-lactamases and *Klebsiella pneumoniae* carbapenemase), and class C β-lactamases (e.g., ampicillin class C cephalosporinase).[8] REL restores the in vitro activity of the carbapenem antibacterial agent imipenem (IPM) against many carbapenem-nonsusceptible isolates of Enterobacterales and *Pseudomonas aeruginosa*.[9–11] REL plus IPM and the renal dehydropeptidase inhibitor cilastatin is approved in the United States for treatment of adults with complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI), and HABP/VABP.[12,13] In the phase III RESTORE-IMI 2 study, imipenem/cilastatin/relebactam (IMI/REL) demonstrated noninferiority to piperacillin/tazobactam for day 28 all-cause mortality and favorable clinical response at the early follow-up visit in adults with gram-negative HABP/VABP.[14]

IPM and REL concentrations do not accumulate over time owing to their short half-lives, and are primarily renally excreted.[15,16] Population pharmacokinetic (PopPK) modeling analyses, using data obtained from healthy participants and participants with cIAI, cUTI, and HABP/VABP, were previously performed to estimate exposure of IPM and REL after single and multiple doses of IMI/REL.[17] Simulations using these models showed that joint probability of target attainment (PTA) for IPM and REL pharmacokinetic (PK)/pharmacodynamic (PD) targets was greater than 90% for minimum inhibitory concentrations (MICs) less than or equal to 2 μg/ml for the 500/250-mg IPM/REL dose, and demonstrated that this dose, with adjustments for impaired renal function, provides adequate antibacterial coverage.[17]

Critically ill patients, including those with HABP/VABP, frequently present with pathophysiological changes that complicate antibacterial dosing. Fluid shifts, renal function changes, and mechanical ventilation can alter the volume of distribution (V_d), maximum concentration (C_{max}), and clearance (CL) of antibacterial agents.[18–21] Whereas participants with HABP/VABP were included in the previously developed models, most data were from healthy participants and participants with cIAI or cUTI. Therefore, further refinement of existing PopPK models with data from participants with HABP/VABP is warranted. In this analysis, the effects of covariates on IPM and REL exposures in patients with HABP/VABP were evaluated using a PopPK model updated with RESTORE-IMI 2 data. To evaluate the RESTORE-IMI 2 dose, the PK/PD joint PTA for IPM and REL among patients with HABP/VABP was also assessed at the 500/250-mg IPM/REL dose.

METHODS

Data sources

Previously described PopPK models, developed using a nonlinear mixed-effects modeling approach, were updated with data from two phase III clinical studies (Table S1).[17] RESTORE-IMI 2 (ClinicalTrials.gov identifier: NCT02493764; protocol MK-7655A-014 [PN014]) was a randomized, double-blind, noninferiority study that evaluated IMI/REL versus piperacillin/tazobactam for the treatment of adult participants with HABP/VABP ($N = 261$).[14] PN014 methodology has been previously described.[14] Briefly, participants were randomized 1:1 to receive IPM/cilastatin/REL 500 mg/500 mg/250 mg or piperacillin/tazobactam 4 g/500 mg, adjusted for renal function (Table S2), every 6 h; efficacy end points included day 28 all-cause mortality and clinical response 7–14 days after completing therapy.[14] In addition to PN014, data from another global, phase III study completed after finalization of the previous PopPK model, PN017 (ClinicalTrials.gov identifier: NCT03293485; protocol MK-7655A-017 [PN017]), were added to this analysis.[22] Additional details regarding the PN014 methodology and the PopPK dataset can be found in the Supplementary Methods.

Modeling methodology

The exploratory analysis, model selection, and integration of PN014/PN017 data steps are described in the Supplementary Methods. The model building methodology is summarized in Figure S1. Clinical and demographic covariates (including body weight, creatinine clearance [CrCl], age, race, infection type [healthy/no infection, cUTI, cIAI, or HABP/VABP], and ventilation status) were included in the data sets to assess their influence on PK characteristics. Covariates were included through a stepwise covariate model building process of forward selection and backward elimination. Covariates were included in the model during the forward addition step if it resulted in a decrease in the objective function value (OFV) of greater than or equal to 6.63 ($p < 0.01$; 1 degree of freedom). For the covariate to remain in the model, during the subsequent backward elimination step, an OFV increase of greater than or equal to 10.83 ($p < 0.001$; 1 degree of freedom) was required. The criteria for assessment of goodness of fit and appropriateness of the covariate model for covariate retention included pharmacological plausibility, decrease in the OFV during forward inclusion and backward elimination, decrease in between-subject variability (BSV) of the affected parameter, graphical inspection of model parameters versus covariate plots, and comparison with the base model without covariates.

The reliability of the final model was evaluated by several methods, including the diagnostic plots described above and goodness-of-fit plots for all relevant data subsets (i.e., infection type and race). Parameter precision was used as a key criterion for model evaluation. Prediction-corrected visual predictive checks (VPCs) of concentration versus time were constructed, and η-shrinkage of empirical Bayesian estimates (EBE) of the model parameters were evaluated to inform relevance of the parameters.[23] A bootstrap analysis was performed to derive the final bootstrap parameter estimates, relative standard errors (SEs), and confidence intervals (CIs) for comparison to nonlinear mixed-effects modeling analysis. An alternative model was used to test the robustness of the final model (Supplementary Methods). The final model was used to perform model-based simulations and to generate individual PK parameter estimates accounting for BSV.

Simulations

The magnitude of covariate effects in the final model was assessed through simulations at the clinical doses of IPM and REL (500/250 mg) corresponding to the 500/500/250-mg IMI/REL dosing used in RESTORE-IMI 2. Descriptions of simulation scenarios used in the simulation of covariate effects are shown in Table 1. Simulations were performed to determine the joint PTA for PK/PD targets of IPM and REL, based on steady-state exposures, to confirm the appropriateness of the current dosing regimens in patients with HABP/VABP with varying levels of renal function.

Data for simulations were compiled from participants with HABP/VABP from PN014. PN014 did not include participants with end-stage renal disease (ESRD); hence, the virtual population for ESRD was constructed from the phase III MODIFY I/II studies (ClinicalTrials.gov identifiers: NCT01241552; NCT01513239). One data pool contained data from participants with nonventilated pneumonia from PN014 ($n = 140$) and participants with ESRD from MODIFY ($n = 38$), and the other contained data from participants with ventilated pneumonia from PN014 (ventilated HABP and VABP [$n = 123$]) and participants with ESRD from MODIFY ($n = 38$). The demographic data, considered representative of the target patient populations, were used to define the variance–covariance matrix between body weight and CrCl. For each pool, a data set of 1,000,000 virtual patients was simulated using the variance–covariance relationship between baseline body weight and baseline CrCl from study participants. From these data sets, patients were randomly selected ($n = 500$ each for each renal category; Table S3)

TABLE 1 Description of simulation scenarios used in the simulation of covariate effects

Group	Description[a]
Reference	Patients, normal renal function (CrCl 90–150 ml/min), weight 70–90 kg
Healthy participant	Healthy participants, normal renal function, weight 70–90 kg
Weight 40–50 kg	Patients, normal renal function, weight 40–50 kg
Weight 50–60 kg	Patients, normal renal function, weight 50–60 kg
Weight 60–70 kg	Patients, normal renal function, weight 60–70 kg
Mild renal impairment	Patients, mild renal impairment (CrCl 60–90 ml/min), weight 70–90 kg
Moderate renal impairment	Patients, moderate renal impairment (CrCl 30–60 ml/min), weight 70–90 kg
Severe renal impairment	Patients, severe renal impairment (CrCl 15–30 ml/min), weight 70–90 kg
Ventilation	Patients, normal renal function (CrCl 90–150 ml/min), weight 70–90 kg, ventilated

Abbreviation: CrCl, creatinine clearance.

[a]Simulations were modeled for patients with hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.

to create independent virtual populations with data sets of 1000 patients with HABP/VABP (ventilated and nonventilated combined) for each renal category. Individual predictions of systemic IPM and REL steady-state exposures were summarized by infection status (healthy participants vs. patients with pneumonia) and ventilation status (ventilated vs. nonventilated).

The IPM susceptibility breakpoints for *P. aeruginosa* and Enterobacterales are less than or equal to 2 μg/ml and less than or equal to 1 μg/ml, respectively, by the US Food and Drug Administration (FDA) and Clinical and Laboratory Standards Institute (CLSI) standards and are less than or equal to 2 μg/ml for both by EUCAST standards.[24,25] For the 500/250-mg IPM/REL and renal function–adjusted dosing regimens described in Table S3, joint PTA at steady-state and adjusted for protein binding was assessed at an MIC breakpoint of less than or equal to 2 μg/ml.[26] For IPM, the PK/PD target was a minimum of 30% of the dosing interval with a plasma-free drug concentration that exceeded the MIC (30% ƒT>MIC).[27] An additional sensitivity analysis using a PK/PD target of 40% ƒT>MIC was also performed. The PK/PD target for REL was a ratio of greater than or equal to 8 for the plasma-free drug area under the concentration–time curve from time 0 to 24 h ($AUC_{0–24}$) normalized to an IPM/REL MIC at a fixed concentration of 4 μg/ml REL ($ƒAUC_{0–24}$/MIC ≥ 8), which is associated with a two-log kill in preclinical models; REL concentration is fixed owing to its lack of intrinsic antibacterial activity.[28–33] Achievement of joint PTA required greater than or equal to 90% of patients to reach PK/PD targets for both drugs.

To evaluate the safety of IPM and REL exposures, simulations were performed to assess the percentage of patients within each renal function group that remained below the upper limit threshold of drug exposure, defined as the 90th percentile of the simulated $AUC_{0–24}$ and C_{max}. For IPM, these exposures were calculated using a dose of 1 g every 6 h in patients with normal renal function (CrCl ≥90 to <150 ml/min); for REL, these exposures were calculated using a dose of 625 mg every 6 h in patients with normal renal function, the highest approved dose for IPM and the highest dose tested in the phase I multiple ascending dose study for REL, respectively.[15,34] For this analysis, greater than 90% of patients were required to remain below the upper exposure threshold for IPM ($AUC_{0–24}$, 3229.8 μM·h; C_{max}, 625.1 μM) and REL ($AUC_{0–24}$, 2941.0 μM·h; C_{max}, 367.9 μM).

RESULTS

Analysis

The addition of 342 participants with quantifiable plasma concentrations included in studies PN014 (n = 261) and PN017 (n = 81) to the 855 participants pooled from 10 prior studies (Table S1) increased the total evaluable participants in the final data set to 1197. These 1197 participants were provided 6100 and 6531 quantifiable IPM and REL plasma concentrations, respectively. In PN014, 3.9% and 2.2% of IPM and REL concentrations were below the limit of quantitation (BLOQ), respectively; there were no data BLOQ in PN017. Across the entire PK data set, concentrations BLOQ were 10.2% and 9.4% for IPM and REL, respectively; however, many BLOQ samples came from four phase I studies, in which subtherapeutic IMI/REL doses were administered and samples were collected at time points beyond the recommended dosing interval of 6 h (up to 24 h after dosing).

Base model

The models for IPM and REL previously described by Bhagunde et al. are two-compartment, zero-order intravenous infusion models with first-order linear elimination.[17]

A model-independent exploratory analysis was performed to confirm that the data from PN014 and PN017 were consistent with prior experience with IPM and REL PKs and these previous models. Spaghetti plots of individual concentration–time profiles observed in PN014, stratified by dose and day, were developed (data not shown). When the median PK profiles were compared by infection type (cIAI/cUTI/nonventilated pneumonia/ventilated pneumonia), participants with pneumonia appeared to have generally similar exposure kinetics for IPM and REL compared with participants with cIAI or cUTI. REL and IPM exposures in participants with pneumonia trended higher than those observed in participants with cIAI or cUTI. Before updating the model with PN014 and PN017 data, external validation with VPCs was conducted and individual predicted concentrations were simulated from the existing model using dosing/covariate and observed concentrations from PN014 and PN017 without refitting the model (Figure S2). These exploratory analyses suggested that the original base model was appropriate for the data set updated with the data from PN014 and PN017.

The BSV of CL, volume of the central compartment (V_1), and volume of the peripheral compartment (V_2) of both IPM and REL were estimated; a proportional error model described the residual error. Outliers that appeared in a preliminary model, developed using the updated data set, were examined, and sequentially excluded from the analysis data set until no further outliers ($-6 \leq$ conditional weighted residuals [CWRES] ≥ 6) were identifiable. When a sensitivity analysis was conducted by including the outliers ($n = 24$), there was no apparent impact of exclusion on the population parameter estimates; however, individual post hoc parameter estimates were impacted for participants who had one or more concentrations excluded as outliers. Therefore, the outliers ($-6 \leq$ CWRES ≥ 6) were excluded from all subsequent analyses. In preparation for the stepwise covariate modeling process, the model was modified by removing the HLTH effect (participant with infection vs. healthy participant) covariate on IPM V_1. The weight exponents on V_1 (IPM and REL) and CL (IPM) were then fixed to estimated values to differentiate between the effects of body weight and race on PK parameters during the stepwise covariate modeling process. The updated base model was used for covariate analysis.

Covariate analysis

Study population characteristics are summarized in Table 2. Before including baseline CrCl as a covariate, an exploratory analysis was performed to identify potential trends in CrCl improvement with treatment and to determine the potential relationship between CrCl change and IPM and REL concentrations 4 h after dosing. No significant trends were identified through this analysis; 13.0% and 12.9% increases in median CrCl were observed on day 3 and day 6, respectively, compared with day 1. Therefore, a time-varying component for the effects of CrCl on IPM and REL PK was not required in model development. As shown for the previously developed PopPK models, and consistent with the renal elimination of IPM and REL, CrCl was a significant covariate on both IPM and REL CL (changes in OFV of −501.7 and −596.6 for IPM and REL, respectively).[17] Body weight was identified as a significant covariate on the CL and V_1 for IPM and the V_1 for REL. These covariates were included in the model a priori. When these covariates were evaluated in the base model, no significant trend in the covariate–EBE plots was noted. Although age and sex were assessed, no trend was observed in the covariate–EBE plots.

There was no deviation from previously observed trends; therefore, covariate models were investigated formally only with respect to new covariates (infection type, ventilation status in pneumonia, and race). Infection type was found to be a significant covariate on the CL and V_1 of both IPM and REL (respective changes in OFV of −154.8 and −52.6 for IPM and −268.0 and −23.8 for REL). Although race was identified as a statistically significant covariate during forward inclusion, it did not meet the required statistical criteria to be retained in the model during backward elimination. Ventilation status was determined to be a significant covariate on the V_1, but not on CL, for IPM and REL (changes in OFV of −11.0 and −21.3 for IPM and REL, respectively).

Final model

After covariate analysis, the model was reparametrized to set healthy participants as the reference group. During this step, a high degree of imprecision with estimating separate thetas was noted, particularly for the cIAI and cUTI groups. Therefore, a new model was developed by grouping together cIAI and cUTI. Weight exponents, which were previously fixed, were re-estimated during the finalization of the model, and the resulting model was comparatively similar with respect to parameter estimates themselves; however, the imprecision associated with estimating multiple infection types was increased, suggesting overparameterization of the model and an inability to estimate all parameters precisely. Therefore, the model was simplified further by grouping participants with cIAI/cUTI with healthy participants to form the reference group while maintaining pneumonia and ventilation status as significant covariates in the model. This

TABLE 2 Clinical and demographic data for study participants

Characteristic	All participants (N = 1,197)
Age, y, median (range)	55 (18–96)
Weight, kg, median (range)	75 (27–180)
CrCl, ml/min, median (range)	106 (8–452)
CrCl category[a]	
<15 ml/min (ESRD)	5 (0.4)
≥15 to <30 ml/min (severe RI)	23 (1.9)
≥30 to <60 ml/min (moderate RI)	143 (12.0)
≥60 to <90 ml/min (mild RI)	277 (23.2)
≥90 to <150 ml/min (normal renal function)	556 (46.6)
≥150 to <180 ml/min (ARC)	131 (11.0)
≥180 to <210 ml/min (ARC)	36 (3.0)
≥210 to <250 ml/min (ARC)	12 (1.0)
≥250 ml/min (ARC)	11 (0.9)
Sex	
Male	733 (61.2)
Female	464 (38.8)
Infection type	
None (healthy)	231 (19.3)
cIAI	308 (25.7)
cUTI	380 (31.7)
Pneumonia	278 (23.2)
Pneumonia type[b]	
Nonventilated HABP	139 (53.3)
Ventilated HABP	30 (11.5)
VABP	92 (35.2)
Race	
White	943 (78.8)
Black/African American	36 (3.0)
Asian (non-Japanese)	23 (1.9)
Asian (Japanese)	123 (10.3)
Asian (Japanese status unknown)	18 (1.5)
Other	54 (4.5)

Note: Data are shown as *n* (%) unless otherwise indicated.

Abbreviations: ARC, augmented renal clearance; cIAI, complicated intra-abdominal infection; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; ESRD, end-stage renal disease; HABP, hospital-acquired bacterial pneumonia; RI, renal impairment; VABP, ventilator-associated bacterial pneumonia.

[a]Three participants had missing CrCl values; therefore, calculated statistics are shown for the remaining 1194 participants.

[b]Based on 261 participants with pneumonia.

yielded the final model, in which all parameters were well estimated.

The final model parameter estimates are shown in Table 3. All parameter estimates had relative SEs below 50%, suggesting acceptable precision. Diagnostic plots for the final model showed that predictions were scattered randomly around the line of unity, indicating an unbiased model, and that observations were in good agreement with population and individual predictions (Figure 1).

The magnitude of the effect of covariates (CrCl, body weight, infection type, and ventilation status) in the final model was assessed through simulations at the clinical doses of IPM (500 mg) and REL (250 mg). For both IPM and REL, the largest covariate effect predicted was based on CrCl as follows: $AUC_{0–24}$ fold change for IPM exposure was 1.23, 1.59, and 2.18 for mild, moderate, and severe renal impairment, respectively, compared with participants with normal renal function; and $AUC_{0–24}$ fold change for REL exposure was 1.39, 2.05, and 3.35 for participants with mild, moderate, and severe renal impairment, respectively, compared with participants with normal renal function. Healthy participants had a lower exposure ($AUC_{0–24}$) compared with participants with pneumonia (fold change of 0.62 and 0.57 for IPM and REL, respectively); these values accounted for differences in body weight and CrCl between the populations (Table 1). Because ventilation status was not a predictor of CL, $AUC_{0–24}$ values for both agents were similar in ventilated participants with pneumonia and nonventilated participants.

Typical model parameter estimates using the final model were comparable with the original base model. An alternate PopPK model in which allometric scaling was used for the effect of body weight on CL and intercompartmental flow rate (Q; fixed to 0.75), as well as V_1 and V_2 (fixed to 1.0), was also assessed. This alternative model yielded similar residual variations among both healthy participants and participants with infections (Table S4). The PTA evaluated using this alternative model did not differ significantly from the PTA obtained using the final model. Thus, the final model was appropriate for the PK data dose justification.

Simulations

Simulations in a combined pneumonia population of nonventilated and ventilated patients (n = 1000 per renal function category) were performed to determine joint PTA for IPM and REL. Joint PTA at steady-state was greater than 99% for patients with HABP/VABP, regardless of renal function category, using targets of 30% ƒT>MIC for IPM and ƒ$AUC_{0–24}$/MIC greater than or equal to 8 for REL at an IPM/REL MIC breakpoint of less than or equal to 2 μg/ml at a fixed concentration of 4 μg/ml REL (Figure 2a). Joint PTA was achieved in a similar proportion of patients across renal function

TABLE 3 Final imipenem and relebactam model parameter estimates

	Imipenem				Relebactam			
	NONMEM		Bootstrap[a]		NONMEM		Bootstrap[a]	
Parameter[c]	Estimate[b] (RSE%)[d]	95% CI[e]	Estimate[b] (RSE%)[d]	95% CI[e]	Estimate[b] (RSE%)[d]	95% CI[e]	Estimate[b] (RSE%)[d]	95% CI[e]
CL (L/h)	12.7 (1.7)	12.3 to 13.1	12.7 (1.7)	12.3 to 13.1	7.23 (1.6)	7.00 to 7.47	7.23 (1.5)	7.03 to 7.45
V_1 (L)	11.4 (3.8)	10.5 to 12.3	11.5 (5.4)	10.3 to 12.7	11.2 (2.7)	10.6 to 11.8	11.2 (2.8)	10.6 to 11.9
V_2 (L)	7.79 (5.7)	6.90 to 8.68	7.76 (7.3)	6.58 to 8.74	6.15 (3.8)	5.68 to 6.62	6.16 (4.1)	5.66 to 6.69
Q (L/h)	23.1 (10.9)	18.0 to 28.1	22.9 (15.2)	16.2 to 29.8	10.9 (7.8)	9.22 to 12.6	10.9 (9.5)	8.82 to 13.1
Covariates on CL								
CrCl (power)	0.48 (4.0)	0.44 to 0.52	0.48 (4.3)	0.44 to 0.52	0.75 (4.2)	0.68 to 0.81	0.75 (4.5)	0.68 to 0.81
WT (power)	0.29 (17.7)	0.19 to 0.39	0.29 (26.1)	0.13 to 0.43	NA	NA	NA	NA
Pneumonia[f]	−0.38 (7.7)	−0.44 to −0.32	−0.38 (7.5)	−0.44 to−0.32	−0.43 (5.0)	−0.48 to−0.39	−0.43 (5.0)	−0.47 to−0.39
Covariates on V_1								
WT (power)	1.03 (9.7)	0.83 to 1.23	1.03 (14.5)	0.75 to 1.31	0.65 (10.7)	0.51 to 0.79	0.66 (12.8)	0.49 to 0.83
Pneumonia[f]	−0.39 (15.5)	−0.52 to−0.27	−0.39 (16.4)	−0.50 to−0.25	−0.29 (16.2)	−0.38 to−0.19	−0.28 (17.8)	−0.38 to−0.18
Ventilation[g]	0.23 (46.2)	0.02 to 0.45	0.24 (47.2)	0.02 to 0.48	0.36 (32.0)	0.13 to 0.58	0.36 (31.8)	0.15 to 0.58
Random effects BSV	**%CV[h] (RSE%) shrinkage**	**95% CI[e]**	**%CV[h] (RSE%)**	**95% CI[e]**	**%CV[h] (RSE%) shrinkage**	**95% CI[e]**	**%CV[h] (RSE%)**	**95% CI[e]**
BSV in CL	53.0 (9.4) 7.2	47.8 to 57.8	53.0 (9.2)	48.0 to 57.4	43.6 (8.1) 13.9	39.9 to 47.0	43.4 (8.1)	40.0 to 46.9
BSV in V_1	86.3 (14.0) 8.7	73.2 to 97.6	86.8 (13.6)	75.5 to 99.0	56.1 (10.1) 18.8	50.1 to 61.6	55.7 (10.7)	50.0 to 61.6
BSV in V_2	63.5 (14.7) 35.6	53.3 to 72.2	63.1 (19.4)	52.9 to 77.5	58.7 (26.2) 49.5	40.5 to 72.5	58.4 (29.8)	40.0 to 76.8
Corr CL ~ V_1[i]	0.97 (11.5)	—	0.97 (11.6)	—	0.62 (12.2)	—	0.62 (12.9)	—
Random effects BSV	**%CV[h] (RSE%) shrinkage**	**95% CI[e]**	**%CV[h] (RSE%)**	**95% CI[e]**	**%CV[h] (RSE%) shrinkage**	**95% CI[e]**	**%CV[h] (RSE%)**	**95% CI[e]**
Residual error, proportional	29.5 (7.4) 14.1	27.2 to 31.6	29.4 (7.3)	26.5 to 31.6	22.6 (6.7) 14.0	21.0 to 24.0	22.5 (6.5)	20.0 to 24.5

Abbreviations: BSV, between-subject variability; CI, confidence interval; CL, clearance; Corr, correlation coefficient; CrCl, creatinine clearance; CV, coefficient of variation; NA, not applicable; NONMEM, nonlinear mixed-effects modeling; Q, intercompartmental flow rate; RSE, relative standard error; V_1, volume of the central compartment; V_2, volume of the peripheral compartment; WT, weight.

[a] Bootstrap is based on $n = 1{,}000$ data set replicates.

[b] Mean parameter estimate.

[c] Imipenem: $CL\ (L/h) = 12.68 \times (CrCl/105.5)^{0.48} \times (WT/75)^{0.29} \times (1+(Flag-0.38_{Pneumonia})) \times \exp(eta_1)$; $V_1\ (L) = 11.39 \times (WT/75)^{1.03} \times (1+(Flag-0.39_{Pneumonia}))_{Pneumonia} \times (1+(Flag-0.23_{Ventilation})) + \exp(eta_2)$; $V_2\ (L) = 7.79 \times \exp(eta_3)$; $Q(L/h) = 23.07$; Relebactam: $CL\ (L/h) = 7.23 \times (CrCl/105.5)^{0.75} \times 0.75\ (1+(Flag-0.43_{Pneumonia})) \times \exp(eta_5)$; $V_1\ (L) = 11.21 \times (WT/75)^{0.65} \times (1+(Flag-0.29_{Pneumonia})) \times (1+(Flag \times 0.36_{Ventilation})) \times \exp(eta_6)$; $V_2\ (L) = 6.15 \times \exp(eta_7)$; $Q(L/h) = 10.93$

[d] RSE% was derived from the following equation: (SE/mean × 100).

[e] 2.5th and 97.5th percentile CIs.

[f] The reference group was healthy participants/participants with complicated intra-abdominal infection/participants with complicated urinary tract infection combined.

[g] The ventilation effect on participants with pneumonia receiving ventilation. The reference group was participants with pneumonia.

[h] Calculated using the following equation: * $\%CV = \sqrt{\omega^2} * 100$.

[i] Corr: correlation between variance parameters calculated as $\omega_{ij}{}^2/\text{sqrt}\left(\omega_{ii}{}^2 * \omega_{jj}{}^2\right)$.

groups, regardless of ventilation status, suggesting that dose adjustment is not necessary for ventilated patients with HABP/VABP (Table S5). A sensitivity analysis using targets of 40% ƒT>MIC for IPM and ƒAUC_{0-24}/MIC greater than or equal to 8 at an IPM/REL MIC breakpoint of less than or equal to 2 μg/ml at a fixed concentration of 4 μg/ml REL resulted in a greater than 98% joint PTA for patients with HABP/VABP (Figure 2b; Table S6).

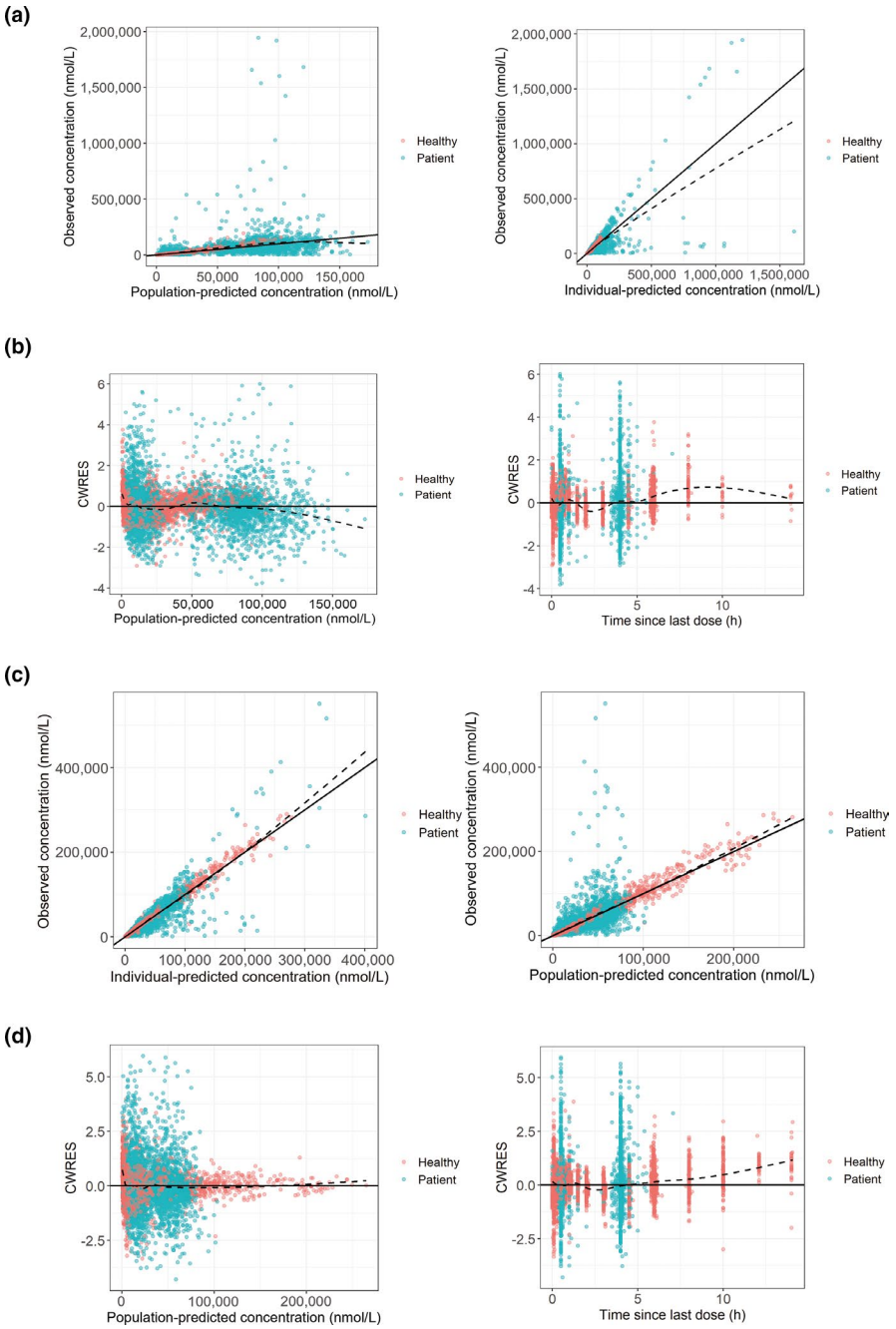

FIGURE 1 Diagnostic plots from the final model for (a, b) imipenem and (c, d) relebactam. Observed concentrations are indicated on the y-axes; predicted concentrations by (a, c [left]) population or (a, c [right]) individual are indicated on the x-axes. CWRES vs. population (left) and CWRES vs. time (right) are presented in b and d. The dashed line denotes smoothing line and the solid line is unity. Circles are individual observations. CWRES, conditional weighted residuals; Healthy, healthy volunteers without infection; Patient, all participants with infection

Individual analyte PTA was greater than or equal to 90% for IPM and REL at targets of 40% ƒT>MIC and ƒ$AUC_{0–24}$/MIC greater than or equal to 8, respectively.

A safety simulation assessed the percentage of patients within each renal function group (n = 1000 per group) that remained within IPM and REL exposure thresholds. As shown in Figure 3, less than 1% of patients in any renal function group exceeded the $AUC_{0–24}$ and C_{max} thresholds when renal function–adjusted doses of IPM/REL were simulated, except the ESRD group in which 12.2% of patients exceeded the threshold for REL $AUC_{0–24}$. However, ESRD (CrCl <15 ml/min) was an exclusion criterion for PN014.[14]

DISCUSSION

We describe the integration of PK data from participants with HABP/VABP treated with IMI/REL in the RESTORE-IMI 2 study into an existing PopPK model to evaluate the effects of covariates on IPM and REL exposures and to analyze PTA in patients with HABP/VABP.[14] These analyses supported final dose selection recommendations for each renal function category in key regulatory approvals for the IMI/REL HABP/VABP indication.

When comparing the original and updated models for IPM, slight differences in V_1, Q, and BSV in V_2 were observed. These changes may be a result of the

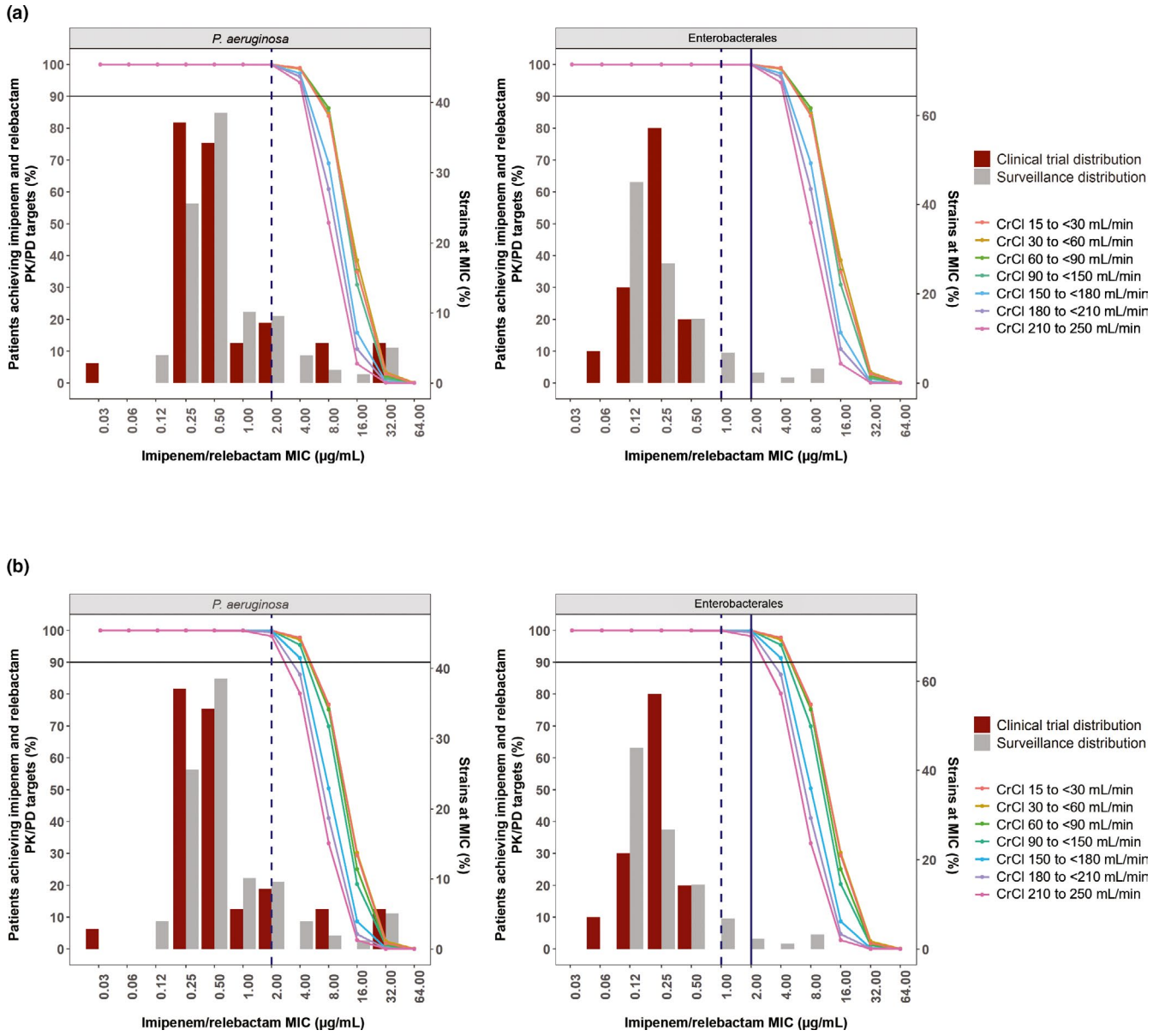

FIGURE 2 Percentage of patients with HABP/VABP that achieved (a) 30% or (b) 40% ƒT>MIC for imipenem and ƒAUC$_{0-24}$/MIC≥8 for relebactam with (left) *Pseudomonas aeruginosa* and (right) Enterobacterales MIC distributions from pneumonia isolates. The percentage of patients that achieved the pharmacokinetic (PK)/pharmacodynamic (PD) targets by renal function group is indicated by the line graphs and the left-sided y-axes. The solid horizontal line represents 90% probability of target attainment. MIC distributions among isolates from PN014 and global surveillance data are indicated by bar graphs and the right-sided y-axes. The dashed vertical line in the left graphs represents an MIC of 2 μg/ml, the dashed vertical line in the right graphs indicates an MIC of 1 μg/ml, and the solid vertical line in the right graphs indicates an MIC of 2 μg/ml. CrCl, creatinine clearance; ƒAUC$_{0-24}$/MIC, free area under the concentration–time curve from time 0 to 24 h normalized to MIC; ƒT>MIC, period of time the free drug concentration exceeded the MIC; HABP/VABP, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; MIC, minimum inhibitory concentration

relatively large variability in IPM exposure observed in participants with HABP/VABP in PN014. VPCs were performed to assess the adequacy of the model fit and were generally in close agreement with observed PK values. However, simulated variability suggested that an overinflated BSV was estimated in healthy participants, which was also noted in the previously published model.[17]

Use of an alternative model with fixed weight exponents for V_1 and CL did not generate significantly different PTA or safety predictions compared with the final model. The diagnostic plot for the REL model indicated a potential bias in the CWRES versus time at approximately greater than or equal to 10 h since the last dose; however, this is unlikely to impact simulation at steady-state at the recommended dose of 500/500/250-mg IMI/REL every

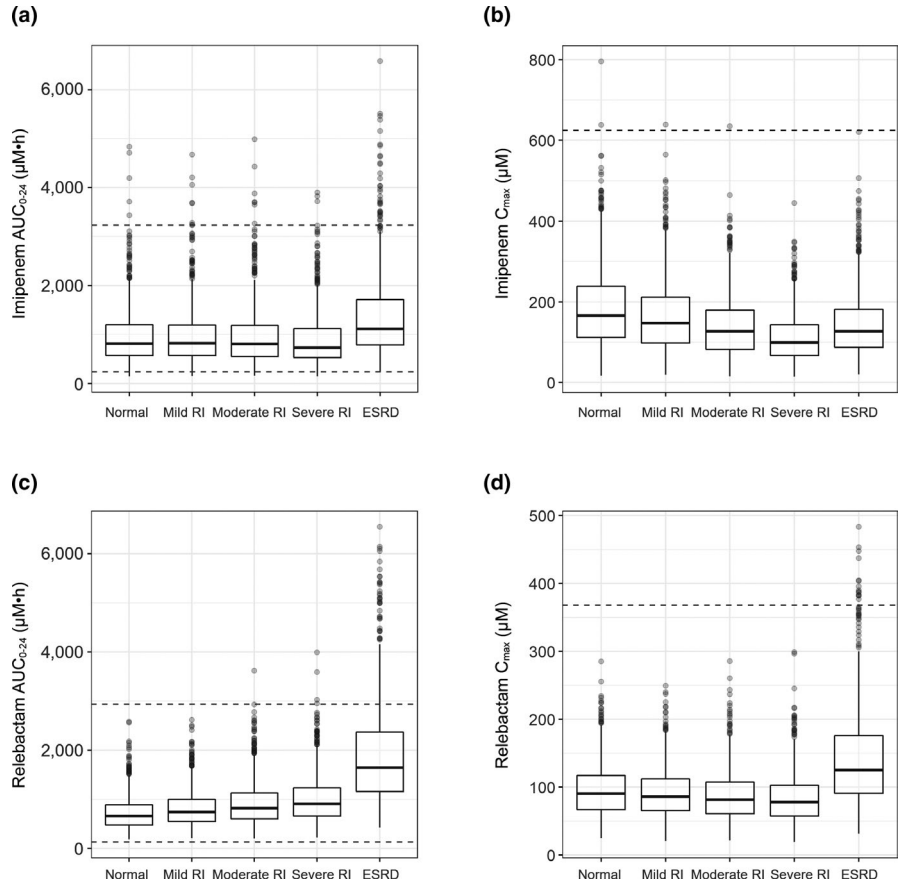

FIGURE 3 Simulated exposures (AUC_{0-24} and C_{max}) for (a, b) imipenem and (c, d) relebactam in patients with HABP/VABP and varying degrees of renal function with imipenem/relebactam administration every 6 h as 30-min intravenous infusions. Steady-state imipenem and relebactam AUC_{0-24} and C_{max} were calculated from simulations conducted using virtual patient populations at the following imipenem/relebactam dosing regimens: normal renal function (CrCl ≥90 to <150 ml/min), 500 mg/250 mg; mild RI (CrCl ≥60 to <90 ml/min), 400 mg/200 mg; moderate RI (CrCl ≥30 to <60 ml/min), 300 mg/150 mg; severe RI (CrCl ≥15 to <30 ml/min), 200 mg/100 mg; and ESRD (CrCl <15 ml/min), 200 mg/100 mg. Boxes represent 25th, 50th, and 75th percentiles; whiskers represent 5th and 95th percentiles; empty circles represent individual AUC_{0-24} or C_{max} values outside the 5th and 95th percentiles. Dashed lines represent 90th percentile of simulated steady-state AUC_{0-24} and C_{max} obtained from a 1000-/625-mg imipenem/relebactam dose administered as a 30-min intravenous infusion in patients with normal renal function. AUC_{0-24}, area under the concentration–time curve from time 0 to 24 hours; C_{max}, maximum concentration; CrCl, creatinine clearance; ESRD, end-stage renal disease; HABP/VABP, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; IMI/REL, imipenem/cilastatin/relebactam; RI, renal impairment

6 h.[12] Because this PopPK model is intended to support dosing in patient populations, the final model is considered appropriate, capturing the updated IPM and REL PK parameters from PN014 while preserving the goodness of fit of previous data.

Altered V_d because of mechanical ventilation has been noted with the antibacterial agents ceftazidime, where mechanical ventilation altered V_2 in patients with *P. aeruginosa* burn infections, and gentamicin, where the apparent V_d was significantly increased in patients who received mechanical ventilation compared with those who breathed spontaneously.[35,36] Ventilation status did not significantly impact the CL of either IPM or REL, as was also observed in gentamicin-treated patients who received ventilation.[36] Thus, these data are consistent with those observed for other antibacterial agents that are primarily excreted renally.[35,36] Correlations observed between body weight and CrCl and between age and CrCl were expected, as the Cockcroft-Gault equation was used to derive CrCl. Race was not identified as a statistically significant covariate; therefore, dose adjustments based on race are not warranted.

To support an optimal dosing regimen and potential dose adjustments for renal function in patients with HABP/VABP, simulations were performed using the final PopPK model to determine the likelihood that patients would achieve a defined joint PK/PD target. These simulations suggested that greater than 90% of patients in all renal function groups should achieve the PK/PD targets of 30% $fT>MIC$ (IPM) and $fAUC_{0-24}/MIC$ greater than

or equal to 8 (REL) with an IPM/REL MIC breakpoint of less than or equal to 2 μg/ml at a fixed concentration of 4 μg/ml REL. Safety simulations also demonstrated that less than 1% of patients in all simulated renal function groups (except ESRD) exceeded the upper threshold for IPM and REL exposures; in patients with ESRD, this value was 12.2% for REL. These simulations demonstrate that dose adjustments in patients with renal impairment, based on CrCl, are adequate to maintain sufficient plasma concentrations for therapeutic efficacy, while maintaining safe exposure levels. These simulations predict that 12.2% of patients with ESRD could exceed the upper exposure threshold observed in the clinical development of IMI/REL. However, there are no known adverse events or safety concerns at or above this upper exposure threshold. Furthermore, the PK simulations for patients with ESRD represent a conservative scenario with the assumption that the drug is not cleared by hemodialysis. Both the favorable safety profile shown in clinical experience and PK simulations described herein support the recommended doses of IMI/REL, adjusted for renal function, in patients with HABP/VABP.[12,14] Additionally, the similar joint PTA results for ventilated and nonventilated patients with pneumonia suggest that dose adjustments are not required for patients with HABP/VABP who receive mechanical ventilation. The results of this joint PTA approach using conservative PK/PD targets support the suitability of the 500/500/250-mg IMI/REL dosing regimen in patients with HABP/VABP.[29,37] This is aligned with a modeling approach for the joint PTA of the β-lactam/β-lactamase inhibitor combination ceftazidime-avibactam.[37]

This analysis has limitations. All BLOQ plasma concentrations in the PK data set were excluded from the analysis; however, most BLOQ concentrations (IPM, 99%; REL, 97%) were from phase I studies, which included a single, and in some studies, lower IMI/REL dose, with PK sampling time points over a longer duration compared with the recommended dosing schedule used in RESTORE-IMI 2. Covariates were assumed to remain at baseline values, which may not be the case for all covariates (e.g., CrCl and ventilation status) in critically ill populations. However, an exploratory analysis of the clinical relevance of CrCl changes observed in PN014 suggested no significant correlation between trough concentration and CrCl change from baseline to day 3 for IPM or REL. Furthermore, the effect of ESRD was based on limited data ($n = 5$ of 1194 individuals), as participants with ESRD were excluded from PN014.[14] Finally, only covariates that were included in the dataset were considered; therefore, it is possible that covariates not included in the dataset may have partially contributed to the differences in results for participants with cIAI, cUTI, and HABP/VABP.

Inclusion of PK data from participants with HABP/VABP in PopPK models indicates that exposures for IPM and REL are higher in these participants compared with healthy participants and participants with cIAI or cUTI. Simulations using these updated models suggest that high and adequate joint PTA is achieved in both ventilated and nonventilated patients with HABP/VABP across all renal function categories. These findings, combined with clinical efficacy and safety data from RESTORE-IMI 2, support the recommended 500/500/250-mg IMI/REL dose with no adjustment based on ventilation status.

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CONFLICTS OF INTEREST

M.P., N.M.D., N.N., D.W.H., K.Y., F.G., and M.L.R. are employees of MSD, and may own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA. F.B., P.K., and W.C. are employees of Certara USA, Inc. or its subsidiaries, which provides consulting services to MSD.

AUTHOR CONTRIBUTIONS

M.P., M.L.R., F.G., and K.Y. designed the research. M.P., F.B., N.M.D., N.N., and D.H. performed the research. M.P., F.B., P.K., W.C., and F.G. analyzed the data. M.P. and F.G. wrote the manuscript.

DATA AVAILABILITY STATEMENT

MSD's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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SUPPORTING INFORMATION

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