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A translational pharmacokinetic/pharmacodynamic model to characterize bacterial kill in the presence of imipenem-relebactam

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ABSTRACT

Objectives: Relebactam is a small molecule β-lactamase inhibitor under clinical investigation for use as a fixed-dose combination with imipenem/cilastatin. Here we present a translational pharmacokinetic/pharmacodynamic mathematical model to support optimal dose selection of relebactam.
Methods: Data derived from *in vitro* checkerboard and hollow fiber infection studies of imipenem-resistant strains of *Pseudomonas aeruginosa* were incorporated into the model. The model integrates the effect of relebactam concentration on imipenem susceptibility in a semi-mechanistic manner using the checkerboard data and characterizes the bacterial time-kill profiles from the hollow fiber infection model data.
Results: Simulations demonstrated that the ratio of the area under the concentration-time curve for free drug to the minimum inhibitory concentration (*f*AUC/MIC) was the pharmacokinetic driver for relebactam, with a target *f*AUC/MIC = 7.5 associated with 2-log kill. At a clinical dose of 250 mg relebactam, greater than 2-log reductions in bacterial load are projected for imipenem-resistant strains with an imipenem/relebactam MIC ≤ 4 μg/mL.
Conclusions: The study confirms that the pharmacokinetic/pharmacodynamic driver for relebactam is *f*AUC/MIC, that an *f*AUC/MIC ratio of 7.5 is associated with 2-log kill in vitro, and that a 250 mg clinical dose of relebactam achieves this target value when delivered in combination with imipenem/cilastatin.

Introduction

A common mechanism of bacterial resistance involves the production of β-lactamase enzyme(s) that can render some β-lactam (BL) antibacterial agents ineffective. β-lactamase inhibitors (BLIs) can inhibit the activity of some of these β-lactamase enzymes, helping to restore bactericidal activity (Drawz and Bonomo, 2010).

Relebactam, a novel non-BL, small molecule BLI with activity against both class A carbapenemases like *Klebsiella pneumoniae* carbapenemases (KPC) and class C cephalosporinases, is being developed as a fixed-dose combination with imipenem/cilastatin (Blizzard et al., 2014; Karlowsky et al., 2018b; Wu et al., 2018). Imipenem is a carbapenem antibacterial agent with coverage of many gram-negative pathogens, including nonfermenters, and certain gram-positive organisms and anaerobes. *In vitro* susceptibility and hollow fiber infection model (HF) time-kill studies showed that relebactam restored activity of imipenem in imipenem-resistant isolates (*Pseudomonas aeruginosa* [class C] and Enterobacteriaceae [new taxonomy: Enterobacterales] that expressed either KPC or extended-spectrum β-lactamases/AmpCs [class A/C, respectively]) (Karlowsky et al., 2018b; Wu et al., 2018). The imipenem/cilastatin-relebactam combination aims to provide a therapeutic option against imipenem-resistant gram-negative pathogens, especially *P. aeruginosa* (class C) and the carbapenemase-producing strains of Enterobacteriaceae (class A).

In vitro susceptibility and HF experiments can provide evidence of preclinical efficacy of BL/BLI combinations (Bhagunde et al., 2012; Wu et al., 2018), with a 1- to 2-log kill in preclinical models associated with clinical outcome (European Medicines Agency, 2016). These data can be integrated in a model-based

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approach and then extrapolated to various untested regimens. Pharmacokinetic/pharmacodynamic (PK/PD) modelling is especially important for a BL/BLI combination since the simultaneous variation in concentration of both components make it challenging to understand the dynamic effect of BL/BLI pharmacokinetics (PK) on bacterial susceptibility and pharmacodynamics (PD) (Wu et al., 2018). The exposure-response relationship for BL/BLI combinations in phase 2/3 clinical studies is difficult to characterize; therefore, *in vitro* and animal models are needed, preferably linked via a quantitative framework that integrates available data. Such a framework can be used to derive the PK/PD driver and optimize the dosing regimen.

Several bacterial susceptibility and HF studies demonstrated that imipenem/relebactam is efficacious against imipenem-resistant *P. aeruginosa* and KPC strains (Bhagunde et al., 2012; Wu et al., 2018). *In vivo* mouse models demonstrated that relebactam efficacy was best correlated with relebactam exposure, demonstrating a concentration-dependent inhibition effect (Mavridou et al., 2015). Here, we integrated *in vitro* studies with human PK data to develop a translational PK/PD model to support the PK driver and clinical dose selection of relebactam. The PK/PD model incorporates the interdependence of the exposure-response relationship between relebactam concentration and imipenem potency, as well as the dynamic response to imipenem/relebactam concentration over time, and simulated human PK of these agents to mimic bacterial killing under clinical dosing regimens.

Materials and methods

Data for model development

The translational PK/PD model included data from *in vitro* checkerboard studies against 87 imipenem-resistant *P. aeruginosa* strains and 13 *in vitro* HF studies conducted against 5 imipenem-resistant *P. aeruginosa* strains. Details of the HF experiments were described previously (Wu et al., 2018).

The HF studies included growth controls, imipenem-only controls, and the imipenem/relebactam combination. Microbiological characteristics of the imipenem-resistant *P. aeruginosa* strains are summarized in Table 1. For each strain, bacteria were exposed to PK profiles of imipenem with or without relebactam to simulate free drug exposure in humans receiving a 30-min infusion of 500 mg imipenem q6h ± 125 mg or 250 mg relebactam q6h, intended to mimic the human half-life and peak concentrations of both compounds. The data (1003 observations) from the HF studies included bacterial colony forming unit (CFU) and PK observations with time for each dosing scenario.

Model structure

The PK/PD model incorporated imipenem-mediated killing of bacteria based on a published PK/PD model (Katsube et al., 2008), with the effect of relebactam incorporated on the minimum inhibitory concentration (MIC) of imipenem.

The relationship between relebactam concentration and the potentiated imipenem MIC was characterized by a nonlinear mixed effect (inhibitory difference between maximum achievable response and baseline effect [E_{max}]) model using a population approach where each strain was treated as an individual. The inhibitory E_{max} (I_{max}) model is estimated across all strains for which the *in vitro* static exposure (checkerboard) studies were conducted. Data were generated using methods adapted from Eliopolous (Eliopolous and Moellering, 1996; Eliopoulos and Wennersten, 2002). Briefly, imipenem was initially evaluated at 2-fold above the expected MIC for each isolate and serially diluted by 2-fold for each row of the plate (highest concentration: 256 μg/mL); relebactam was diluted by 2-fold for each column of the plate (highest concentration: 64 μg/mL). Plates were scored for bacterial growth and the concentrations of antibacterial agent and BLI where no growth was evident were used to determine extent of synergy.

The population estimates of I_{max} and half maximal inhibitory concentration (IC_{50}) were used to characterize the change in imipenem MIC in the presence of relebactam (Bhagunde et al., 2012), which results in a dynamically changing potency of imipenem against the bacteria. The bacterial population is assumed to adapt or become resistant to imipenem pressure and the adaptation is dependent on imipenem concentration, time, rate of adaptation (τ), and maximum extent of adaptation (β). The potency of imipenem is a combination of dynamically changing imipenem MIC in the presence of relebactam and bacterial adaptation to imipenem. Bacterial killing by imipenem is a function of the dynamic imipenem potency (KC_{50}) and maximum kill rate (K_{max}). A schematic of the PK/PD model is shown in Figure 1 and displays the interplay between imipenem, relebactam, and bacteria. The killing effect of imipenem only acts toward the growth compartment (actively dividing bacteria) and not on the latent compartment (bacteria in the resting state).

Model estimation

In vitro static exposure (checkerboard) experiment data were used to characterize the relationship between relebactam and potentiated imipenem MIC by the I_{max} model using the following equation:

$$MIC = MIC_0\left(1 - \frac{I_{max}C_{REL}}{IC_{50} + C_{REL}}\right),$$

where MIC_0 is the baseline (unpotentiated) MIC for each strain, I_{max} is the maximum inhibitory effect of relebactam on imipenem MIC, IC_{50} is the concentration of relebactam required to reach half-maximal inhibition, and C_{REL} is the time-varying concentration of relebactam. Since the change in imipenem MIC with relebactam was different for different bacterial strains, inter-strain variability

Table 1
Imipenem-resistant strains evaluated in the hollow fiber infection model and included in translational PK/PD model development.

Organism	Isolate	Imipenem MIC (μg/mL)	Imipenem/Relebactam MIC (μg/mL)[a]	AmpC Expression Fold Change[b]
P. aeruginosa	CLB 24226	32	4	1.3
P. aeruginosa	CLB 24227	16	2	13.6
P. aeruginosa	CLB 24228	32	8	35.0
P. aeruginosa	CLB 24354	64	16	.84
P. aeruginosa	CL 5701	16	2	1.4

Adapted from Wu 2018 with permission (Wu et al., 2018).
MIC, minimum inhibitory concentration; PK/PD, pharmacokinetics/pharmacodynamics.
[a] Imipenem/relebactam MIC is measured in the presence of 4 μg/mL relebactam.
[b] Fold change in AmpC expression in the presence of imipenem. The AmpC induction assay used is described in Livermore 2017 (Livermore et al., 2017).

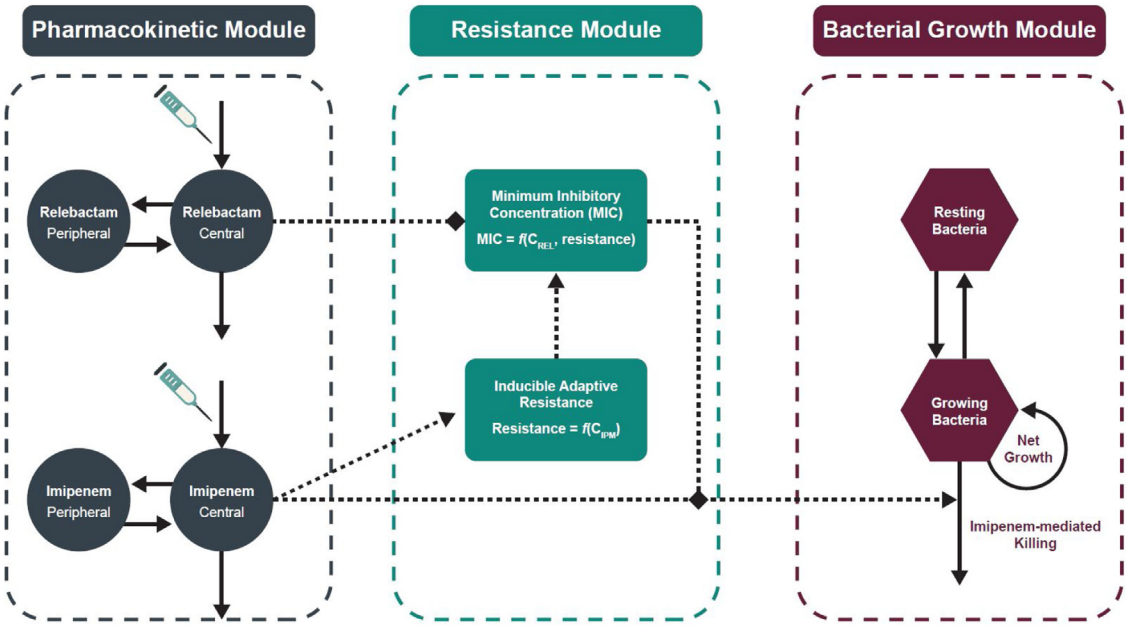

Figure 1. Schematic representation of various modules in the translational pharmacokinetics/pharmacodynamics model. $f\,C_{REL}$, free drug concentration of relebactam; $f\,C_{IPM}$, free drug concentration of imipenem.

was accounted for as a random effect (ETA) on I_{max} and IC_{50} in the model as follows:

$$I_{max} = TVI_{max}(exp(ETA1)),$$

$$IC_{50} = TVIC_{50}(exp(ETA2)),$$

where TV is the typical value for I_{max} and IC_{50}.

A logistic growth model was then used to characterize the bacterial growth curves observed in growth control experiments. The equations used to fit the HF bacterial growth profiles were:

$$\frac{dN_g}{dt} = K_g\left(1 - \frac{N_g}{N_{max}}\right)N_g - K_{gr}N_g + K_{rg}N_r,$$

$$\frac{dN_r}{dt} = K_{gr}N_g - K_{rg}N_r,$$

$$N = N_g + N_r,$$

where N equals the total bacterial population (CFU/mL), N_{max} is the maximum bacterial population at which growth saturates (CFU/mL), N_g is the bacterial population in the growing state (CFU/mL), N_r is the bacterial population in resting state (CFU/mL), K_g is the bacterial growth rate, K_{rg} is the rate of bacterial transfer from resting to growing state, and K_{gr} is the rate of bacterial transfer from growing to resting state. To account for variability in maximum growth, interindividual variability was applied as a random effect to N_{max} as follows:

$$N_{max} = TVN_{max}(exp(ETA1))$$

Finally, bacterial killing and adaptation effects were estimated by fitting the model to bacterial kill data from a range of *in vitro* HF studies using the following equations:

$$\alpha = 1 + \beta\left(1 - e^{-C_{IPM}t\tau}\right),$$

$$F_{EC50} = 0.0813MIC\alpha,$$

$$\frac{dN_g}{dt} = K_g\left(1 - \frac{N_g}{N_{max}}\right)N_g - K_{gr}N_g + K_{rg}N_r - \frac{K_{max}C_{IPM}}{F_{EC50} + C_{IPM}}(N_g),$$

$$\frac{dN_r}{dt} = K_{gr}N_g - K_{rg}N_r,$$

where α is the bacterial adaptation factor, β is the maximum extent of bacterial adaptation, τ is the rate of bacterial adaptation, F_{EC50} is the potency of imipenem as a function of bacterial adaptation and potentiated MIC, K_{max} is the maximum kill rate by imipenem, C_{IPM} is the concentration of imipenem, t is the time, with other variables as previously defined.

To estimate these parameters, the imipenem MIC dependence on relebactam concentration was fixed using the population estimates of the I_{max} model above. To account for variability in HF bacterial kill profiles, inter-individual variability is applied on specific bacterial system parameters as K_{max}, β, and τ as follows:

$$K_{max} = TVK_{max}(exp(ETA1))$$

$$\beta = TV\beta(exp(ETA2)),$$

$$\tau = TV\tau(exp(ETA3))$$

For purposes of model estimation, K_g, K_{max}, β, and τ were estimated. To avoid identifiability issues, some of the model parameters were fixed to values within literature-reported ranges. Specifically, K_{rg} and K_{gr} were fixed to literature reported values, $0.024\,h^{-1}$ and $0.566\,h^{-1}$, respectively (Katsube et al., 2008). Final model estimates are summarized in Table 2.

The PK of imipenem and relebactam in the HF system were described using a one-compartment PK model. Clearance was back calculated using the simulated half-life (1.5 h for imipenem and

Table 2
Translational PK/PD model parameter estimates.

Parameter	Units	Estimate (% RSE)	IIV as % CV
I_{max}	–	0.944 (0.74)	3.6
IC_{50}	μg/mL	0.533 (10.2)	85.9
K_g	h^{-1}	1.13 (8.3)	–
K_{gr}	h^{-1}	0.024 (fixed)	–
K_{rg}	h^{-1}	0.566 (fixed)	–
N_{max}	$log10_{10}$ CFU/mL	9.94 (0.67)	2.56
K_{max}	h^{-1}	4.34 (0.9)	28.3
β	–	40 (4.7)	32.6
τ	L/mg h	0.0099 (7.07)	63.2

β, maximum extent of adaptation; CFU, colony forming unit; CV, percent coefficient of variation; IIV, interindividual variability; I_{max}, maximum inhibitory effect of relebactam on imipenem minimum inhibitory concentration; IC_{50}, inhibitory concentration required to reduce activity by 50%; K_g, bacterial growth rate; K_{gr}, rate of bacterial transfer from growing to resting state; K_{rg}, rate of bacterial transfer from resting to growing state; K_{max}, maximum kill rate; N_{max}, maximum bacterial population at which growth saturates in absolute CFU/mL; PK/PD, pharmacokinetics/pharmacodynamics; RSE, relative standard error; τ, rate of adaptation.

relebactam), while volume was set to the HF central compartment volume. The back calculated clearance and volume were validated on the PK obtained from the HF system and fixed when estimating the model parameters.

All model fitting was done using the first-order conditional estimation (FOCE) with Laplacian conditional with interaction method in nonlinear mixed effects modelling (NONMEM Version 7.3.0) and Perl-speaks-NONMEM (PsN, Version 4.2.0). A proportional residual error was assumed during model development. Observations below the limit of quantification were handled using Beal's M3 method. Postprocessing of the output was conducted using R (Version 3.3.1).

Model stability and qualification of the final model were assessed by goodness of fit (GOF) diagnostics, parameter estimates close to literature observed/physiologically possible values, and parameter (θ) estimates not close to boundary values. Once estimated, the model was validated using visual predictive checks.

Simulations

Simulations of *in silico* relebactam dose-response and dose-fractionation were conducted in combination with a fixed imipenem dose of 500 mg q6h, both as a 30-min infusion. The objective of this *in silico* study was to determine the relebactam PK/PD driver and its magnitude. The PK/PD model was used to simulate varying degrees of bacterial kill in the HF model with PK of both imipenem and relebactam kept as observed in the HF system, as previously described.

The relebactam total daily dose ranged from 0–3000 mg (0 [imipenem-alone treatment], 250, 500, 1000, 2000, and 3000 mg). At each dose level, the dosing interval varied between 1.5–24 h. For all simulations, imipenem was maintained at 500 mg q6h. The baseline bacterial load was assumed to be 10^5 CFU/mL, and the population estimates of the I_{max} model and the PK/PD model described in Table 2 were used. A PK/PD relationship was explored between 24-h change in bacterial log(CFU/mL) from baseline and various relebactam PK parameters: area under the concentration-time curve for free drug (*f*AUC), *f*AUC/MIC, maximum drug concentration (fC_{max}), fC_{max}/MIC and %*f*T > Ct (Ct = 1, 2, or 4 μg/mL), where Ct was the threshold concentration. These threshold concentrations were selected based on historic data for BLIs (Bradford and Sanders, 1993; Singh et al., 2015; Vanscoy et al., 2013) and to ensure an adequate spread of the data. The PK parameter that provided the best relationship as suggested by coefficient of determination (R^2) value was determined to be the PK/PD driver. The magnitude of the PK driver was the value that resulted in stasis, 1-log, and 2-log kill in bacterial load at 24 h.

Additional simulations were conducted to project the relebactam clinical exposure-response while keeping the imipenem dose at 500 mg (both were dosed q6h as 30-min infusion) in order to confirm optimal dose selection for phase 2 and 3 studies. In these simulations, PK was simulated using human PK parameters estimated from population PK models for imipenem and relebactam (Bhagunde et al., 2019; Rhee et al., 2018; Wu et al., 2018). Human PK for both imipenem and relebactam were described using 2 compartment models. Only the population estimates of the PK parameters were used to simulate the typical human PK for subjects with normal renal function (creatinine clearance = 90 mL/min) and average body weight (70 kg). Imipenem and relebactam were assumed to be 80% and 78% free to calculate free drug levels.

Results

Model development

The parameter estimates and standard errors were reasonable considering both physiological plausibility and model stability (Table 2). The overlay plots of model predictions (individual predictions [IPRED] and predictions [PRED] with dependent variable observations [DV]) show close agreement between the model predictions and observations. The PRED values describe the mean tendency in bacterial load change with time and mean tendency of imipenem MIC change with relebactam for the I_{max} model. This is also evident in PRED vs DV plots (Supplementary Material, Figure S1), and demonstrates the appropriateness of interindividual variability in predicting parameters for each subject.

Conditional weighted residuals (CWRES) revealed no trends with PRED or time and are evenly distributed around the line of zero (Supplementary Material, Figure S2). Overall, the parameter estimates and GOF plots show that the I_{max} model can describe the change in imipenem MIC with relebactam concentration across strains, the logistic growth model can describe bacterial growth curves across strains, and the PK/PD model can describe the bacterial kill curves for various dosing regimens of imipenem/relebactam. Visual predictive checks stratified by dosing regimen indicated that the final model could predict the median and distribution of bacterial load reasonably well, and the proportion of observations below the lower limit of quantification.

Simulations

In silico dose fractionation simulations demonstrate that the parameter most closely associated with response (the relebactam PK/PD driver) is the area under the concentration-time curve from 0–24 h ($AUC_{0\text{-}24h}$)/MIC (Figure 2), where the MIC is the potentiated MIC in the presence of 4 μg/mL relebactam. The 4 μg/mL susceptibility testing concentration is based on the average free concentration in patients with normal renal function (4.4 μg/mL). This is consistent with findings in a murine thigh model, which suggested that efficacy was best correlated with AUC (Mavridou et al., 2015). The magnitude of the PK/PD driver ($fAUC_{0\text{-}24h}$/MIC) required for stasis, 1-log, and 2-log kill are 2.7, 4.7, and 7.5, respectively. The majority of patient exposures at a 250 mg dose of relebactam are well above the $fAUC_{0\text{-}24h}$/MIC ratio of 7.5, and are sufficient to provide >2-log kill for imipenem-resistant strains with imipenem/relebactam MIC ≤ 4 μg/mL, suggesting a 250 mg dose of relebactam is optimal.

Additional simulations leveraging the clinical population PK models to derive the exposure-response relationship demonstrate that a relebactam $fAUC_{0\text{-}24h}$ of 42 μM h is sufficient to obtain 2-log

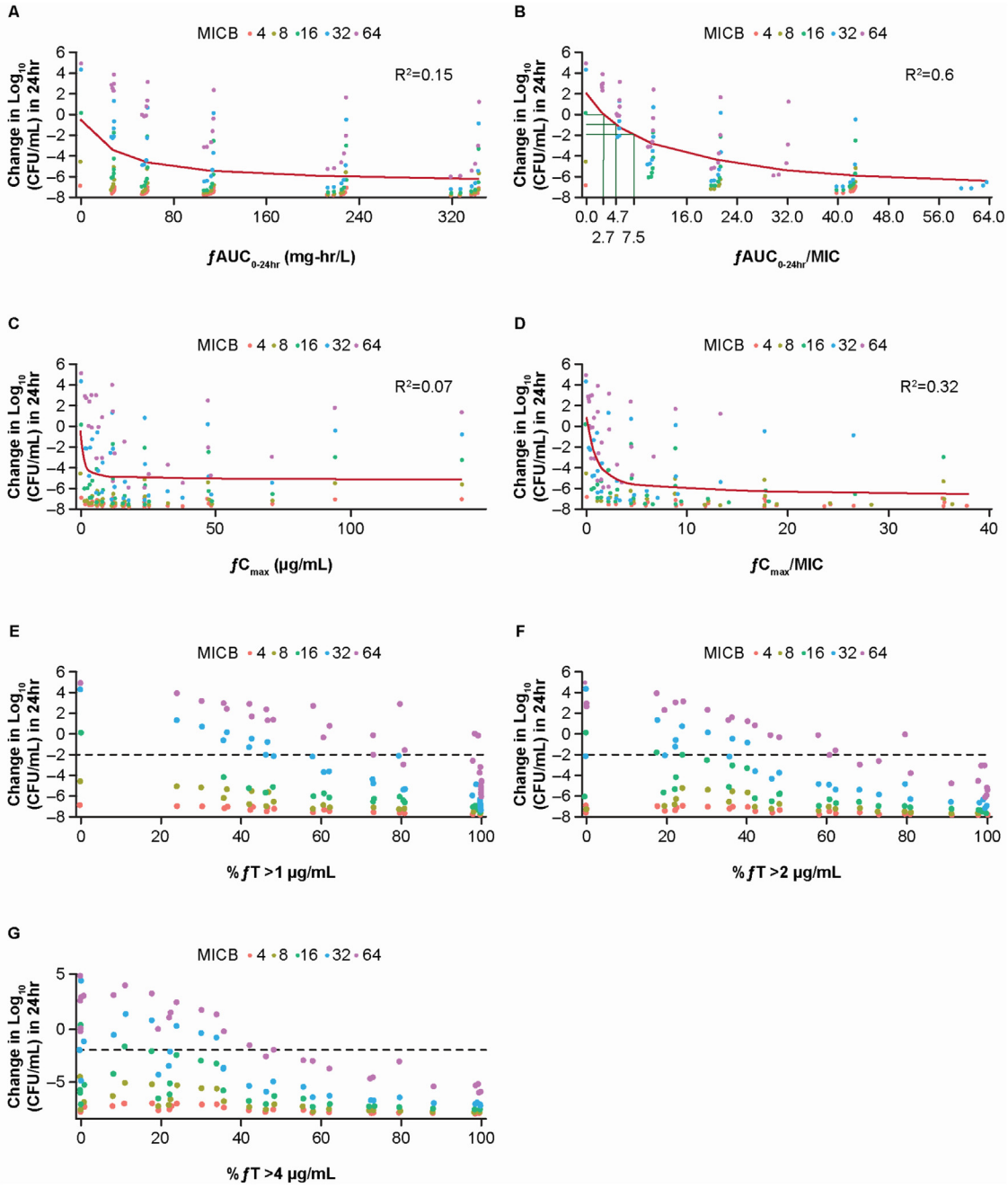

Figure 2. Relebactam pharmacokinetics/pharmacodynamics relationships in hollow fiber infection model system with varying doses of relebactam (total daily doses of 0–3000 mg administered every 1.5 to 24 h [q1.5h – q24h]) in combination with 500 mg imipenem q6h in *P. aeruginosa* strains with MICB values ranging from 4–64 µg/mL. Regression analysis could not be performed for panels E, F, and G.
*f*AUC$_{0\text{-}24h}$, area under the free concentration-time curve from 0–24 h; CFU, colony forming unit; *f*C$_{max}$, maximum free drug concentration; MIC, minimum inhibitory concentration; MICB, unpotentiated MIC; %*f*T, percent of time free concentration is higher than given threshold.

kill for imipenem-resistant strains with imipenem/relebactam MIC $\leq$ 4 µg/mL (potentiated MIC obtained in the presence of 4 µg/mL relebactam; Figure 3; to convert to mg h/L, multiply by 0.34848). A comparison of the distribution of 250 mg relebactam human clinical exposures (*f*AUC$_{0\text{-}24h}$) from previous clinical studies showed that exposures for all patients are above this target and thus would be sufficient to provide $\geq$2-log kill for imipenem-resistant strains with imipenem/relebactam MIC $\leq$ 4 µg/mL. These data support the selection of a 250 mg clinical dose of relebactam.

Overall, these results suggest that imipenem-resistant strains with imipenem/relebactam MICs of $\leq$4 µg/mL can be treated effectively with imipenem/relebactam at the proposed dosing regimen of 500 mg/250 mg q6h as a 30-min infusion. A combined assessment of surveillance studies found that 93.3% of all *P. aeruginosa* strains have imipenem/relebactam MICs $\leq$4 µg/mL. Among the subset of imipenem-resistant strains, 75% have imipenem/relebactam MICs $\leq$4 µg/mL and thus should be treated effectively by imipenem/relebactam (Karlowsky et al., 2018a; Lob et al., 2017).

Discussion

Clear dose- and exposure-response relationships for BL/BLI combinations are difficult to assess given our limited ability to

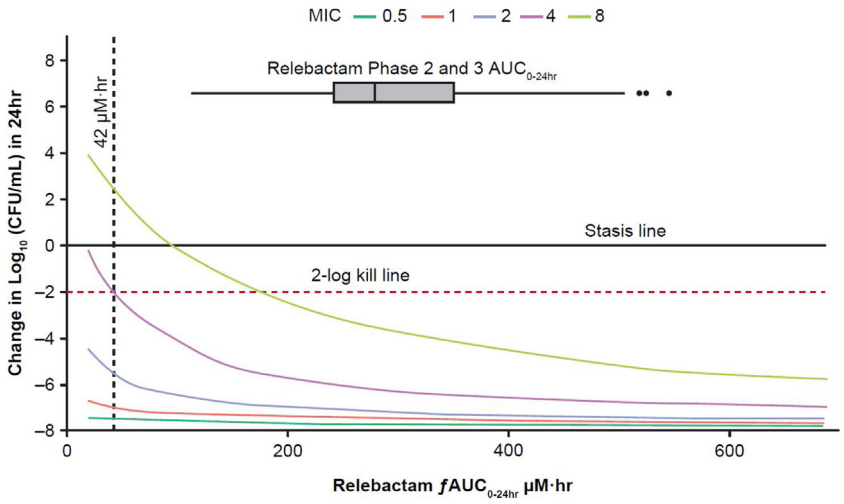

Figure 3. Exposure-response relationship for bacterial kill at 24 h postinitiation of therapy at varying doses of relebactam in combination with 500 mg imipenem every 6 h (q6h) in *Pseudomonas aeruginosa* strains with imipenem/relebactam minimum inhibitory concentration (MIC) values ranging from 0.5–8 μg/mL. Phase 2 and 3 AUC was calculated for normal renal function patients who received 250 mg relebactam q6h. The horizontal box plot represents 25th percentile, median, and 75th percentiles, with whiskers representing the 5th and 95th percentiles. To convert μM h to mg h/L, multiply by 0.34848.
f$AUC_{0\text{-}24h}$, area under the concentration-time curve for free drug from 0–24 h; CFU, colony forming unit.

conduct dose-ranging studies in the clinic. *In vitro* susceptibility and time-kill information is needed to characterize PK/PD and project clinical doses. Here we developed a PK/PD mathematical model using information from *in vitro* susceptibility and HF studies. The model adequately described bacterial response to imipenem/relebactam in the HF system, and the model was useful to derive the relebactam PK/PD driver and its magnitude.

The effect of relebactam on bacterial susceptibility to imipenem was incorporated by characterizing the change in imipenem MIC in the presence of increasing concentrations of relebactam. In the presence of time-varying concentrations of relebactam, imipenem MIC becomes dynamic, thereby contributing to imipenem's dynamic potency (Bhagunde et al., 2012). The presence of relebactam lowers imipenem MIC, hence lowering the concentration of imipenem at which half of the maximum effect is observed (median effective concentration). Correlating BL MIC with potency has been shown to be appropriate (Mouton and Vinks, 2005), as all bacterial killing is accomplished by imipenem, and relebactam increases the susceptibility of bacteria to imipenem (Drawz and Bonomo, 2010). Another important factor in the model is bacterial adaptive resistance to imipenem, whose functional form has been previously presented (Tam et al., 2005). While relebactam acts to counter resistance caused by β-lactamase production, bacteria can become resistant via other mechanisms or multiple mechanisms simultaneously (Drawz and Bonomo, 2010). The inclusion of adaptive resistance is necessary to incorporate the impact of other mechanisms of resistance on imipenem potency (Tam et al., 2005).

In silico dose fractionation simulations demonstrate that the relebactam AUC normalized by MIC is the PK/PD driver best linked to efficacy. This has also been observed with the BLI vaborbactam (Griffith et al., June 1-5, 2017). In contrast, avibactam and tazobactam are reported to be driven by the percent time above a threshold concentration (Berkhout et al., 2016; Crandon and Nicolau, 2013; Nicasio et al., 2016). This difference in PK/PD drivers could be due to altered enzyme-binding kinetics. Relebactam is a mechanism-based inhibitor that is practically irreversible, in that the turnover number is close to 1 and approaches the turnover rate of a classical mechanism-based inactivator. Thus, the degree of β-lactamase inhibition should be governed by inhibition kinetics, which is a function of relebactam concentration and exposure time, rather than the maintenance of a critical concentration, as would be the case for a reversible inhibitor (Blizzard et al., 2014). In contrast, avibactam, while not inactivated (hydrolyzed or chemically rearranged) like other BLIs, is a covalently bound and reversible BLI (Ehmann et al., 2012). Restoration of antibacterial activity of BLs by avibactam was reported to be time-dependent rather than concentration-dependent and was more closely linked to time above the threshold concentration (*f*$T > C_T$) than exposure (*f*AUC) (Nichols et al., 2018).

The PK/PD driver and its magnitude were also consistent with conclusions from *in vivo* mouse studies, which concluded that relebactam PK/PD is AUC-driven (Mavridou et al., 2015). The utility of the PK/PD model is to capture the effects of imipenem and relebactam when exposures fluctuate with time, and allow derivation of PK/PD targets at relevant clinical dosing regimens. The model was limited to *P. aeruginosa* strains, as infections due to *P. aeruginosa* are generally more difficult to treat and require higher drug exposures compared with infections due to Enterobacteriaceae; thus, an imipenem/relebactam dose that effectively treats infections from *P. aeruginosa* will also be effective against Enterobacteriaceae strains (eg, KPCs) at similar MICs, in that the latter require much lower levels of relebactam for enzyme inhibition (Blizzard et al., 2014; Wu et al., 2018; Young et al., 2010).

Development of such a dynamic PK/PD model has several advantages over traditional empirical approaches for deriving PK/PD targets. This framework allows for integration of all available time-course data of both PK and bacterial load, rather than relying on a single time point (e.g., 24 h) for bacterial response. Future extensions of such a framework could include incorporating murine *in vivo* data (to explore consistency between *in vitro* and *in vivo* systems), exploring the impact of bacterial inoculum on the PK/PD parameters, and additional mechanistic details around enzyme kinetics to explore the relationship between enzyme inhibition parameters and the corresponding PK/PD driver for BLIs.

Conclusions

The study confirms that the PK/PD driver for relebactam is *f*AUC/MIC and that an *f*AUC/MIC ratio of 7.5 is associated with 2-log kill *in vitro.* Additionally, characterization of the relebactam exposure-response was accomplished by incorporating clinical PK data into the PK/PD model simulations, which also demonstrate that the relebactam clinical dose of 250 mg q6h (with 500 mg imipenem q6h) was at the plateau of exposure-response and that

the distribution of clinical exposures were above levels associated with 2-log kill for strains up to imipenem/relebactam MICs of 4 μg/mL. These data provided justification for the relebactam dose of 250 mg q6h selected for clinical development.

Conflict of interest

PB, ZZ, FR, DC, JW, KY, MLR are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co, Inc., Kenilworth, NJ, USA (MSD), and may own stock and/or stock options in the company.

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Ethics approval

Not applicable.

Authors' contributions

All authors are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design of work or acquisition, analysis, interpretation of data; drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.08.026.

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