

# The Pharmacokinetics/Pharmacodynamic Relationship of Durlobactam in Combination With Sulbactam in In Vitro and In Vivo Infection Model Systems Versus *Acinetobacter baumannii-calcoaceticus* Complex

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Sulbactam-durlobactam is a  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination currently in development for the treatment of infections caused by *Acinetobacter*, including multidrug-resistant (MDR) isolates. Although sulbactam is a  $\beta$ -lactamase inhibitor of a subset of Ambler class A enzymes, it also demonstrates intrinsic antibacterial activity against a limited number of bacterial species, including *Acinetobacter*, and has been used effectively in the treatment of susceptible *Acinetobacter*-associated infections. Increasing prevalence of  $\beta$ -lactamase-mediated resistance, however, has eroded the effectiveness of sulbactam in the treatment of this pathogen. Durlobactam is a rationally designed  $\beta$ -lactamase inhibitor within the diazabicyclooctane (DBO) class. The compound demonstrates a broad spectrum of inhibition of serine  $\beta$ -lactamase activity with particularly potent activity against class D enzymes, an attribute which differentiates it from other DBO inhibitors. When combined with sulbactam, durlobactam effectively restores the susceptibility of resistant isolates through  $\beta$ -lactamase inhibition. The present review describes the pharmacokinetic/pharmacodynamic (PK/PD) relationship associated with the activity of sulbactam and durlobactam established in nonclinical infection models with MDR *Acinetobacter baumannii* isolates. This information aids in the determination of PK/PD targets for efficacy, which can be used to forecast efficacious dose regimens of the combination in humans.

**Keywords.** pharmacokinetics/pharmacodynamics; *Acinetobacter*; sulbactam; durlobactam; diazabicyclooctane.

*Acinetobacter baumannii* is increasingly associated with serious nosocomial infections often accompanied by high rates of morbidity and mortality [1–4]. The majority of *A. baumannii* isolates are multidrug-resistant (MDR), resulting in limited treatment options [5]. Carbapenem-resistant *A. baumannii* has been identified as a global threat and has been designated as an urgent unmet medical need, requiring new treatment options [6, 7]. Sulbactam-durlobactam (SUL-DUR) is being developed for the treatment of *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections, including those caused by MDR *A. baumannii*.

## CLINICAL USE OF SULBACTAM TO TREAT ACINETOBACTER INFECTIONS

Sulbactam is commonly used to treat *A. baumannii* infections due to its ability to inhibit penicillin-binding proteins (PBP1 and PBP3) in *Acinetobacter* spp., leading to cell death of the bacteria [8]. Clinically, *Acinetobacter* infections have been successfully treated with a high-dose 2:1 combination of ampicillin:sulbactam. Although some in vitro studies have suggested that ampicillin and sulbactam may act synergistically [9], clinical studies utilizing sulbactam administration alone suggest that the intrinsic activity of sulbactam is responsible for the observed efficacy of this combination versus *A. baumannii* infections encountered clinically [10]. As described below, these observations have also been supported in experimental infection models conducted in in vitro and in vivo studies [11–19].

## SULBACTAM EFFICACY OBSERVED IN ANIMAL INFECTION MODELS

In a neutropenic murine lung infection model, the efficacy of sulbactam was evaluated following administration of a 100-mg/kg dose every 3 hours (q3h) versus a susceptible *A. baumannii* isolate, SAN-94040, with a sulbactam minimum inhibitory concentration (MIC) of 0.5  $\mu$ g/mL and a less-susceptible isolate, RCH-69, with a sulbactam MIC of 8  $\mu$ g/mL

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[13]. The mice were rendered neutropenic and treatment was initiated 3 hours after infection of the lung. Treatment was conducted for 12 hours (4 doses of sulbactam administered intraperitoneally) and lungs were harvested 3 hours after the final dose to assess bacterial burden. Drug concentrations were determined systemically as well as in the lung. Serum concentrations of sulbactam were above the MIC for more than 3 hours vs SAN-94040 and 1.7 hours vs RCH-69. In the lung, concentrations of sulbactam exceeded the MIC for 4.8 and 1.3 hours for SAN-94040 and RCH-69, respectively. These treatments translated to end-of-treatment lung tissue burdens of  $4.31 \pm 0.19$  and  $6.4 \pm 1.3 \log_{10}$  colony-forming units (CFU)/g for SAN-94040 and RCH-69, respectively. Vehicle controls grew greater than  $7 \log_{10}$  CFU/g for both isolates. A bactericidal effect with a greater than  $2\text{-log}_{10}$  CFU reduction from baseline was observed for SAN-94040 but not RCH-69. These findings were largely consistent with the pulmonary concentrations of sulbactam, which remained above the MIC of SAN-94040 for the entire dosing interval, but only above the MIC of RCH-69 for 43% of the dosing interval [13].

More recent studies have provided a rigorous assessment of the pharmacokinetic/pharmacodynamic (PK/PD) index most correlated with sulbactam activity and unbound exposure magnitude requirements to achieve PK/PD endpoints of net bacterial stasis and 1-, 2-, and 3- $\log_{10}$  CFU reductions from baseline in neutropenic murine thigh and lung infection models versus *A. baumannii* American Type Culture Collection (ATCC) 19606 [14]. This isolate was both sulbactam- and carbapenem-sensitive, with an MIC of 0.5  $\mu\text{g}/\text{mL}$  for both sulbactam and imipenem. Dose fractionation was performed in both thigh and lung models over a dose range of 15 to 240 mg/kg administered at 2-, 3-, 4-, 6-, 12-, and 24-hour intervals. Comparison of Hill-type model fits describing the relationship between 24-hour change in  $\log_{10}$  CFU/g burden and PK/PD indices of the time during 24 hours that unbound concentrations remain above the MIC ( $fT > \text{MIC}$ ), the ratio of unbound area under the concentration-time curve over 0 to 24 hours to the MIC ( $f\text{AUC}_{0-24}/\text{MIC}$ ), and the ratio of unbound maximum concentration to the MIC ( $fC_{\text{max}}/\text{MIC}$ ) demonstrated correlation coefficients ( $R^2$ ) of 0.95, 0.60, and 0.37, respectively. Based on this analysis, the PK/PD index most closely associated with sulbactam activity was  $fT > \text{MIC}$ . The magnitude of sulbactam  $fT > \text{MIC}$  associated with achieving net bacterial stasis (no net change in bacterial counts over 24 hours of treatment) and 1-, 2-, and 3- $\log_{10}$  CFU reductions from baseline is summarized in Table 1. These magnitudes of  $fT > \text{MIC}$  were largely consistent with imipenem, which was used as a comparator in the study. Slightly higher potency was observed for sulbactam in the lung model compared with the thigh, with approximately 20%  $fT > \text{MIC}$  for a static effect and more than 60% and more than 40%  $fT > \text{MIC}$  for bactericidal effects in the thigh and lung, respectively.

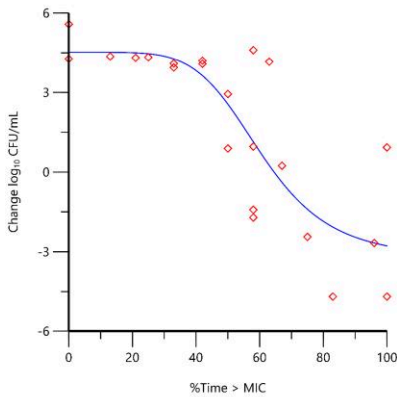
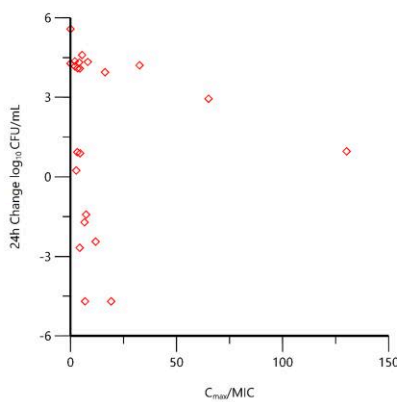
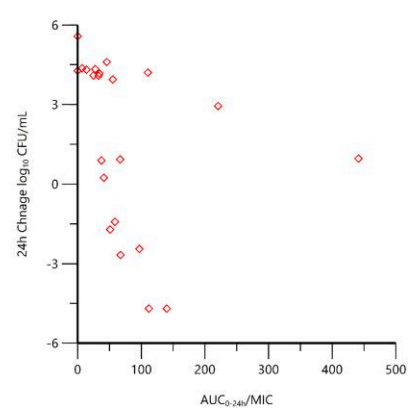
**Table 1. Magnitude of Sulbactam  $fT > \text{MIC}$  Associated With Net Bacterial Stasis, and 1-, 2-, and 3- $\log_{10}$  CFU Reductions From Baseline Against *Acinetobacter baumannii* in Thigh and Lung Models**

Bacterial Reduction Endpoint	Sulbactam $fT > \text{MIC}$ (%) by Mouse Infection Model	
	Thigh	Lung
Net bacterial stasis	21.0	20.4
1- $\log_{10}$ CFU reduction from baseline	32.9	24.5
2- $\log_{10}$ CFU reduction from baseline	43.6	29.3
3- $\log_{10}$ CFU reduction from baseline	57.3	37.3

Data from reference [14].  
Abbreviations: CFU, colony-forming units;  $fT > \text{MIC}$ , time that unbound drug concentration remains above the minimum inhibitory concentration.

### SULBACTAM PK/PD TARGETS ESTABLISHED FROM IN VITRO INFECTION MODELS

The magnitude of  $fT > \text{MIC}$  associated with sulbactam efficacy was further investigated in in vitro dynamic model systems simulating the sulbactam component of 2:1 ampicillin:sulbactam human PK exposures in an evaluation of MDR *A. baumannii* isolates ranging in sulbactam MIC values of 2 to 32  $\mu\text{g}/\text{mL}$  [15]. Free-drug concentrations of sulbactam from 3 g ampicillin/sulbactam (2 g/1 g) every 6 hours (q6h) (0.5-hour infusion) and 9 g ampicillin/sulbactam (6 g/3 g) every 8 hours (q8h) (3-hour infusion) were evaluated in a one-compartment in vitro PK/PD model over 24 hours to determine the net change in  $\log_{10}$  CFU/mL from baseline as well as the area under the bactericidal curve (AUBC). Both the 3-g q6h and the 9-g q8h regimens provided exposure consistent with 100%  $fT > \text{MIC}$  compared with the MDR isolate, ACB 35 (MIC = 2  $\mu\text{g}/\text{mL}$ ), and resulted in sustained bactericidal activity over the 24 hours of the experiment. The lower dose of 3 g demonstrated minimal efficacy versus ACB 32 (MIC = 32  $\mu\text{g}/\text{mL}$ ), with an observed  $fT > \text{MIC}$  of only 5.9%. Nearly a 1- $\log_{10}$  CFU reduction from baseline was achieved versus ACB 31 and ACB 33 (MIC = 16  $\mu\text{g}/\text{mL}$ ), with an observed  $fT > \text{MIC}$  of approximately 29%. Results for the higher 9-g dose regimen were variable but still not effective compared with ACB 32 ( $fT > \text{MIC}$  of 50.7%), although higher AUBCs were achieved across all the isolates relative to the lower 3-g dose regimen. It was suggested that higher  $fT > \text{MIC}$  exposure may be needed in vitro to maintain efficacy or a higher concentration of sulbactam itself to circumvent higher  $\beta$ -lactamase production associated with the MDR isolates [15]. Additional studies were undertaken using a hollow-fiber in vitro infection model to reconfirm the PK/PD index associated with sulbactam efficacy and the magnitude of such an index required for various levels of bacterial reduction (O'Donnell et al., Unpublished data). High magnitudes of sulbactam  $fT > \text{MIC}$  associated with net bacterial stasis and 1- and 2- $\log_{10}$  CFU/mL reductions from baseline were observed in dose-fractionation studies, whereas lower sulbactam

**A** %T>MIC ( $r^2 = 0.82$ )**B**  $C_{max}/MIC$  ( $r^2 = 0.44$ )**C**  $AUC_{0-24}/MIC$  ( $r^2 = 0.67$ )

**Figure 1.** The 24-hour change in *Acinetobacter baumannii* Astra research collection (ARC)2058 (ADC-99 [N379S]; oxacillinase [OXA]-259) CFU/mL relative to sulbactam time (T) > MIC (A),  $C_{max}/MIC$  (B), and  $AUC_{0-24}/MIC$  (C) based on data from a hollow-fiber in vitro infection model (O'Donnell et al., Unpublished data): (A) %T > MIC ( $r^2 = 0.82$ ); (B)  $C_{max}/MIC$  ( $r^2 = 0.44$ ); (C)  $AUC_{0-24}/MIC$  ( $r^2 = 0.67$ ). Red diamond symbols represent PK parameter estimates derived from each dose fractionated regimen vs. the change in bacterial burden over 24 hours. The line represents the non-linear regression analysis of the data using the Hill equation. Abbreviations:  $AUC_{0-24}$ , area under the concentration-time curve over 0 to 24 hours; CFU, colony-forming units;  $C_{max}$ , maximum concentration; MIC, minimum inhibitory concentration.

exposure magnitudes of sulbactam  $fT > MIC$  associated with these endpoints were observed in in vivo models. Consistent with results from previous studies, however,  $fT > MIC$  was identified as the PK/PD index most closely associated with the activity of sulbactam (Figure 1). The reason for the higher magnitudes of  $fT > MIC$  in the hollow-fiber in vitro system is still unknown. However, the lower molecular weight cutoff (5 kD) of the hollow-fiber cartridge may trap and accumulate  $\beta$ -lactamases, which we have confirmed through nitrocefin assay of cartridge contents (J. O'Donnell 2023, unpublished data). This potentially serves as a sink for sulbactam, reducing the amount of unbound drug available to interact with PBPs as well as reducing the targeted concentration of the  $\beta$ -lactam in the system—a phenomenon observed by other investigators [16, 17]. To avoid this, further studies were carried out to determine the magnitude of sulbactam  $fT > MIC$  associated with efficacy in in vitro chemostat and in vivo neutropenic murine infection models, in which the concentration of  $\beta$ -lactamase does not confound interpretation of study results (O'Donnell et al., Unpublished data).

In vivo studies completed to support the PK/PD understanding of sulbactam and durlobactam were carried out using neutropenic murine thigh and lung infection models and contemporary *A. baumannii* clinical isolates with relevant resistance determinants spanning a broad range of MIC values (O'Donnell et al., Unpublished data). Initial dose-ranging studies based on mouse PK and sulbactam susceptibility (with and without durlobactam) suggested that a 4:1 dose ratio of sulbactam:durlobactam from 2.5:0.625 mg/kg to 80:20 mg/kg administered every 3 to 6 hours would be sufficient to explore PK/PD relationships for efficacy [18]. Dose titration in a 4:1 ratio

dosing of sulbactam:durlobactam was completed versus MDR *A. baumannii* strain ARC3486 (OXA-66, OXA-72, Temoneria [TEM]-1, acinetobacter-derived cephalosporinase [ADC]-30), which had a sulbactam MIC of 32  $\mu\text{g}/\text{mL}$  or greater. In the presence of a 4- $\mu\text{g}/\text{mL}$  concentration of durlobactam, the sulbactam MIC versus ARC3486 was reduced to 0.5  $\mu\text{g}/\text{mL}$ . Initial tissue burden at the time of treatment was 6.36  $\log_{10}$  CFU/g in the thigh model and 7.40  $\log_{10}$  CFU/g in the lung model. In vehicle (no treatment) controls, colonies grew approximately 2  $\log_{10}$  CFU from baseline over 24 hours. At the top dose of 80:20 sulbactam:durlobactam q3h, a greater than 2  $\log_{10}$  CFU/g reduction was achieved over 24 hours in both models, with a clear dose-response observed across the dose range. An additional study was performed in the neutropenic murine thigh infection model utilizing a 15-mg/kg dose of sulbactam q3h across all dose arms and titrating the durlobactam dose from 1.25 to 50 mg/kg in combination. The 15-mg/kg dose was identified in PK studies to be consistent with unbound sulbactam concentrations exceeding an MIC (of sulbactam alone) of 0.5  $\mu\text{g}/\text{mL}$  for 50% of the dosing interval, an exposure associated with achieving a 1- $\log_{10}$  CFU or greater reduction from baseline across the infection models completed in vitro and in vivo (Table 2) (O'Donnell et al., Unpublished data). Sulbactam administered alone at a dose of 15 mg/kg q3h was ineffective and nearly equivalent to the vehicle (no treatment) control. This observation was expected, as the MIC of sulbactam alone versus ARC3486 was 32  $\mu\text{g}/\text{mL}$  or greater. The addition of durlobactam resulted in a clear dose-dependent reduction from baseline bacterial burden ( $\log_{10}$  CFU/g), with near maximal activity observed at a dose of 15:5 mg/kg sulbactam:durlobactam administered q3h. Similar studies using a

**Table 2. Magnitude of Sulbactam  $fT > MIC$  Associated With 1- and 2-Log<sub>10</sub> CFU Reductions From Baseline and EC<sub>80</sub> Based on Data From In Vitro and In Vivo Studies**

Model	No. of Isolates	$r^2$	Sulbactam $fT > MIC$ (%) by Endpoint		
			CFU Reduction From Baseline		EC <sub>80</sub>
			1-Log <sub>10</sub>	2-Log <sub>10</sub>	
In vitro hollow fiber <sup>a</sup>	1	0.82	71.5	82.0	93.6
In vivo thigh (4:1 dose) <sup>b</sup>	6	0.83	29.9	38.2	44.1
In vivo lung (4:1 dose) <sup>c</sup>	5	0.89	41.2	53.5	>100
Mean $\pm$ SD	...	...	47.5 $\pm$ 21.5	57.9 $\pm$ 22.2	68.9 $\pm$ 35.0

Data from reference (O'Donnell et al., Unpublished data). EC<sub>80</sub>, the percentage of time required for unbound concentrations to remain above the MIC in order to achieve 80% of the maximum activity.  
Abbreviations: CFU, colony-forming units;  $fT > MIC$ , time that unbound drug concentration remains above the minimum inhibitory concentration; SD, standard deviation  
<sup>a</sup>Sulbactam-sensitive isolate *A. baumannii* ARC2058.  
<sup>b</sup>Single pooled dataset Hill-type fitting across 6 *A. baumannii* isolates; sulbactam:durlobactam, 4:1.  
<sup>c</sup>Single pooled dataset Hill-type fitting across 5 *A. baumannii* isolates; sulbactam:durlobactam, 4:1.

higher fixed dose of sulbactam to cover a higher SUL-DUR MIC of 4  $\mu\text{g}/\text{mL}$  were also completed [19]. The MDR *A. baumannii* strain used in these investigations, ARC5955 (TEM-1, ADC-82, OXA-23, and OXA-66), had a sulbactam MIC of 64  $\mu\text{g}/\text{mL}$ , but activity was restored to an MIC of 4  $\mu\text{g}/\text{mL}$  with the addition of durlobactam. A dose of 75 mg/kg q3h was evaluated across all dose arms in a neutropenic murine thigh infection model, with increasing doses of durlobactam added from 12.5 to 200 mg/kg. The sulbactam dose of 75 mg/kg was selected to achieve  $fT \geq 4 \mu\text{g}/\text{mL}$  for greater than 50% of the dosing interval. Neither sulbactam nor durlobactam administered by themselves at 75 and 50 mg/kg, respectively, q3h were effective, with 2.5- and 2.2-log<sub>10</sub> CFU/g growth observed over 24 hours. Net bacterial stasis was achieved when 12.5 mg/kg of durlobactam was added to sulbactam (75 mg/kg) and a 1-log<sub>10</sub> CFU reduction from baseline was observed when the durlobactam dose was increased to a dose of 50 mg/kg. Another half-log<sub>10</sub> CFU/g reduction from baseline was achieved when a 200-mg/kg dose of durlobactam was added to sulbactam (75 mg/kg).

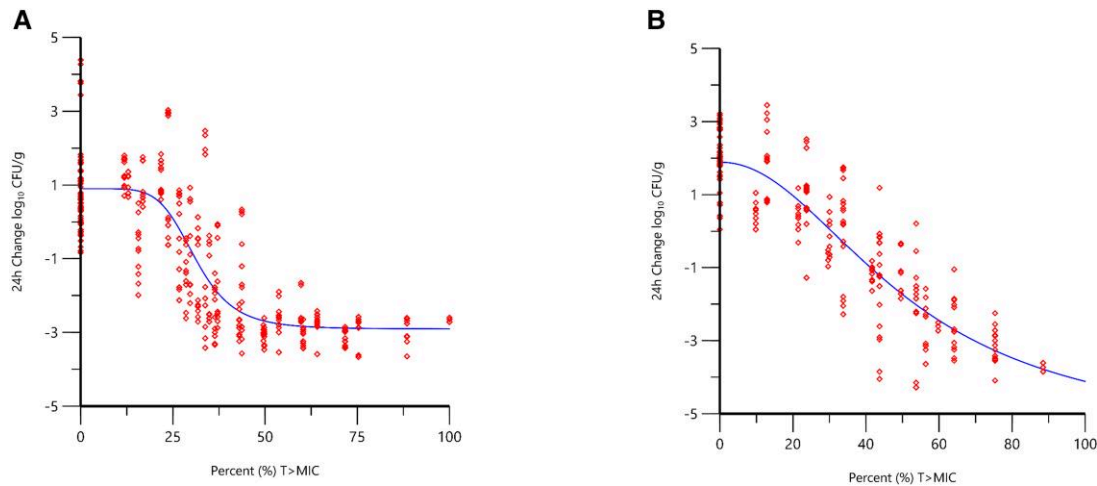
### DURLOBACTAM PK/PD TARGETS ESTABLISHED FROM A ONE-COMPARTMENT IN VITRO INFECTION MODEL

Having established a PK/PD target of approximately 50%  $fT > MIC$  for sulbactam, further in vitro studies were pursued using a one-compartment chemostat model to determine the PK/PD index and magnitude of such an index associated with durlobactam activity (O'Donnell et al., Unpublished data). Several recent publications have investigated the PK/PD of contemporary  $\beta$ -lactamase inhibitors, reporting that the PK/PD index most closely associated with activity was either unbound concentrations exceeding a critical threshold ( $C_T$ ) or unbound  $\text{AUC}_{0-24}/\text{MIC}$ . It has been suggested that the type of inhibition observed biochemically with the inhibitor may provide insight

into the optimum PK/PD index associated with its activity [20, 21]. The PK/PD of the  $\beta$ -lactamase inhibitor tazobactam, which demonstrates a relatively slow on rate and slow off rate appears to be driven by  $fT > C_T$  [22]. By contrast, nearly irreversible inhibitors such as vaborbactam [23] and relebactam [24] may benefit from a time-exposure and concentration dependency associated typically with mechanism-based inactivators demonstrating greater affinity and rapid on rates [21]. For these inhibitors, the AUC may be a more relevant parameter associated with the inhibitor-enzyme interaction and target occupancy [25]. Durlobactam inhibition of class D  $\beta$ -lactamases, which are highly prevalent in *A. baumannii* isolates, has been shown to be particularly potent with  $k_{\text{inact}}/K_i$  values nearly 1000-fold higher than avibactam [18, 26] and a partition ratio of nearly 1 against the vast majority of  $\beta$ -lactamases [27]. With these types of covalent interactions, inhibition would be expected to increase over time with exposure as opposed to reaching equilibrium. Based on these observations, one might expect  $f\text{AUC}/\text{MIC}$  to be the PK/PD driver for durlobactam.

Studies in the one-compartment system were carried out using a single MDR *A. baumannii* isolate, ARC5081, which demonstrated a sulbactam MIC of 16  $\mu\text{g}/\text{mL}$  and an MIC of 4  $\mu\text{g}/\text{mL}$  for sulbactam in the presence of 4  $\mu\text{g}/\text{mL}$  of durlobactam (O'Donnell et al., Unpublished data). Initial dose-ranging studies with sulbactam administered q6h at clinically equivalent exposures of 2 g administered every 6 hours combined with durlobactam administered q6h with a durlobactam  $f\text{AUC}_{0-24}$  range of 18.5 to 591  $\mu\text{g} \cdot \text{hour}/\text{mL}$  were performed prior to dose fractionation with durlobactam. Dose fractionation was then completed using durlobactam  $f\text{AUC}_{0-24}$  of 13.9, 55.8, 111, and 222  $\mu\text{g} \cdot \text{hour}/\text{mL}$  administered every 6, 12, or 24 hours. For all studies, sulbactam and durlobactam were administered into the system via a 3-hour infusion. At sulbactam 2 g q6h, the time above the SUL-DUR MIC of 4  $\mu\text{g}/\text{mL}$  exceeded 50% of the dosing interval. The relationships between each





**Figure 2.** Change in bacterial burden ( $\log_{10}$  CFU/g) over 24 hours vs % $fT > MIC$  of sulbactam when administered alone and combined with durlobactam based on data from neutropenic murine thigh ( $r^2 = 0.83$ ,  $n = 6$  isolates) (A) and lung ( $r^2 = 0.89$ ,  $n = 5$  isolates) (B) infection models (O'Donnell et al., Unpublished data). Red diamond symbols represent PK parameter estimates derived from each dose fractionated regimen vs. the change in bacterial burden over 24 hours. The line represents the non-linear regression analysis of the data using the Hill equation.

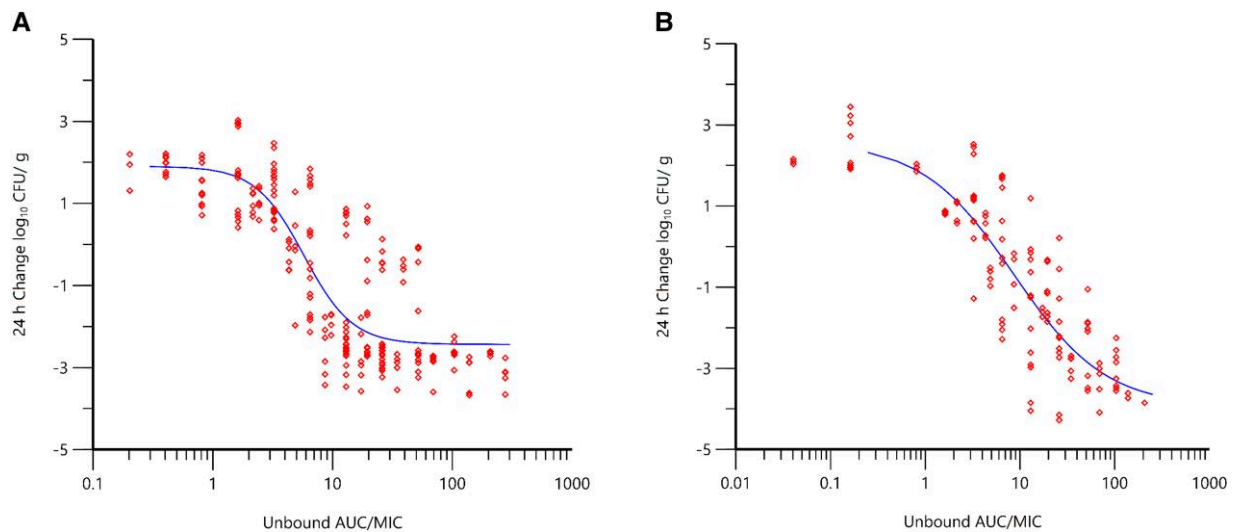
Abbreviations: CFU, colony-forming units;  $fT > MIC$ , time that unbound drug concentration remains above the minimum inhibitory concentration; MIC, minimum inhibitory concentration.

of durlobactam  $AUC_{0-24}$ ,  $C_{max}$ , and the percentage of time that durlobactam concentrations were above the  $C_T$  values ranging from 0.5 to 2  $\mu\text{g/mL}$  and the 24-hour change in  $\log_{10}$  CFU/g were evaluated using Hill-type models and nonlinear least-squares regression. Fitting of the data demonstrated that free time above a critical threshold ( $fT > C_T$ ) of 0.75  $\mu\text{g/mL}$  was most highly correlated to the observed activity of durlobactam when administered in combination with sulbactam. While time-dependent activity is associated with the PK/PD of durlobactam, the half-life of the compound precludes a meaningful analysis of the dose-fractionation data to establish PK/PD targets clinically. When only the q6h and q12h data were considered, however,  $AUC_{0-24}$  was considered a more informative PK/PD index, with data scattered equally across the Hill-type function and a clear maximum effect observed (O'Donnell et al., Unpublished data). Because a q6h regimen of sulbactam is required clinically to achieve its PK/PD target of 50%  $fT > MIC$ , a q6h durlobactam regimen was considered. Based on the Hill-type model fit of  $fAUC_{0-24}$  versus 24-hour change  $\log_{10}$  CFU/mL and administration of durlobactam q6h, 1- and 2- $\log_{10}$  CFU reductions from baseline were associated with  $fAUC_{0-24}$  of 30.5  $\mu\text{g} \cdot \text{h/mL}$  and 134  $\mu\text{g} \cdot \text{h/mL}$ , respectively, versus ARC5081. Using the modal SUL-DUR MIC of 4  $\mu\text{g/mL}$  for ARC5081, these exposures correspond to  $fAUC_{0-24}$ : MIC ratios of approximately 10 and 30 for 1- and 2- $\log_{10}$  CFU reductions from baseline, respectively. In summary, while the PK/PD of durlobactam was shown to demonstrate time-dependent activity in vitro,  $fAUC_{0-24}/MIC$  was shown to correlate to activity using the q6h and q12h dosing, likely due to the short half-life of the compound.

## SULBACTAM AND DURLOBACTAM PK/PD TARGET MAGNITUDES ESTABLISHED IN VIVO

Pharmacokinetic/pharmacodynamic analyses for both sulbactam and durlobactam were performed utilizing data for multiple *A. baumannii* isolates evaluated using neutropenic murine thigh and lung infection models. Isolates were selected with the goal to evaluate a broad range of MIC values below and above the projected breakpoint of 4  $\mu\text{g/mL}$ . Although MDR bacteria can exhibit a number of resistance mechanisms, in the case of carbapenem-resistant *Acinetobacter*, the prevailing resistance mechanism is  $\beta$ -lactamase production. It follows that bacteria with higher MIC values likely have higher expression levels of  $\beta$ -lactamase and, thus, would require higher  $\beta$ -lactamase inhibitor exposure to effectively restore wild-type MIC distribution of the  $\beta$ -lactam. Thus, a direct translational relationship should exist between inhibitor exposure and the MIC. This has been shown in the evaluation of the  $\beta$ -lactamase inhibitor tazobactam used in combination with ceftolozane, for which co-modeling of 7 isolates was performed by normalizing the % $fT > C_T$  by the MIC, where the  $C_T$  was the product of the ceftolozane-tazobactam MIC for each individual isolate multiplied by 0.5 [28]. Thus, pooled and co-modeled data spanning a broad range of MIC were considered together to arrive at a single exposure target directly related to in vitro susceptibility of the isolate.

A sulbactam-sensitive *A. baumannii* isolate, ARC2058, was used in neutropenic murine thigh and lung infection models to compare the magnitude of sulbactam  $fT > MIC$  associated with efficacy in the thigh and lung for sulbactam treatment alone. In the lung model, the mean  $fT > MIC$  magnitudes required for a 1- $\log_{10}$  and 2- $\log_{10}$  CFU reduction from baseline



**Figure 3.** Change in bacterial burden ( $\log_{10}$  CFU/g) over 24 hours vs  $fAUC_{0-24}/MIC$  of durlobactam when administered in combination with sulbactam based on data from neutropenic murine thigh ( $r^2 = 0.86$ ,  $n = 5$  isolates) (A) and lung ( $r^2 = 0.91$ ,  $n = 4$  isolates) (B) infection models (O'Donnell et al., Unpublished data). Red diamond symbols represent PK parameter estimates derived from each dose fractionated regimen vs. the change in bacterial burden over 24 hours. The line represents the non-linear regression analysis of the data using the Hill equation.

Abbreviations: CFU, colony-forming units;  $fAUC_{0-24}/MIC$ , ratio of unbound area under the concentration-time curve over 0 to 24 hours to the minimum inhibitory concentration.

**Table 3. Magnitude of Durlobactam  $fAUC_{0-24}/MIC$  Associated With 1- and 2- $\log_{10}$  CFU Reductions From Baseline and  $EC_{80}$  Based on Data From In Vitro and In Vivo Studies**

Model	No. of Isolates	$r^2$	Durlobactam $fAUC_{0-24}/MIC$ by Endpoint		
			CFU Reduction From Baseline		$EC_{80}$
			1- $\log_{10}$ CFU Reduction	2- $\log_{10}$ CFU Reduction	
In vitro chemostat <sup>a</sup>	1	0.87	7.6	33.4	NC
In vivo thigh (4:1 dose) <sup>b</sup>	5	0.86	8.0	16.0	15.1
In vivo lung (4:1 dose) <sup>c</sup>	4	0.91	10.6	22.4	78.6
In vivo thigh (fixed SUL dose) <sup>d</sup>	6	0.82	7.5	31.8	38.2
Mean $\pm$ SD	...	...	$8.4 \pm 1.5$	$25.9 \pm 8.2$	$44.0 \pm 32.1$

Data from reference (O'Donnell et al., Unpublished data). PK-PD analysis of 24-hour net CFU reduction vs  $fAUC_{0-24}/MIC$ .  $EC_{80}$ , the percentage of time required for unbound concentrations to remain above the MIC in order to achieve 80% of the maximum activity.

Abbreviations: CFU, colony-forming units;  $fAUC_{0-24}/MIC$ , ratio of unbound area under the concentration-time curve over 0 to 24 hours to the minimum inhibitory concentration; NC, not calculated; PK/PD, pharmacokinetic/pharmacodynamic; SD, standard deviation; SUL, sulbactam.

<sup>a</sup>SUL exposure at  $>50\%$   $fT > MIC$ .

<sup>b</sup>SUL mean exposure of 32.9% to 43.5%  $fT > MIC$ ; sulbactam:durlobactam, 4:1.

<sup>c</sup>SUL mean exposure of 43.9% to 81.5%  $fT > MIC$ ; sulbactam:durlobactam, 4:1.

<sup>d</sup>SUL exposure range of 18.2% to 52.7%  $fT > MIC$ ; sulbactam dose held constant.

and the exposure required to reach 80% of maximum activity ( $EC_{80}$ ) were 37.8%, 50.1%, and 68.5%, respectively. In the thigh model, mean  $\%fT > MIC$  magnitudes required for a 1- $\log_{10}$  and 2- $\log_{10}$  CFU reduction from baseline and the  $EC_{80}$  were 20.5%, 31.5%, and 47.0%, respectively. These magnitudes were close to exposures associated with efficacy of sulbactam in human clinical studies [10, 29–31] when considering human PK parameters for sulbactam [32, 33].

Up to 5 recent MDR *A. baumannii* clinical isolates, for which the  $\beta$ -lactamase genotypes had previously been determined by

whole-genome sequencing (ARC3484, ARC3486, ARC5079, ARC5081, and ARC5091), were evaluated in addition to ARC2058 in dose–response studies conducted using neutropenic murine thigh and lung infection models. These studies were carried out to determine the  $\%fT > MIC$  magnitudes required by sulbactam when administered in the presence of durlobactam (O'Donnell et al., Unpublished data). Co-modeling of the  $\%fT > MIC$  sulbactam exposure response data across multiple MDR isolates and ARC2058 was performed utilizing the data obtained from both neutropenic thigh and lung models

incorporating 4:1 sulbactam:durlobactam administration (Figure 2). The 24-hour change in CFU/g from the initiation of therapy versus  $fT > MIC$  for the pooled dataset of all isolates used in each model was fit to a Hill-type function, and the magnitude of sulbactam  $fT > MIC$  targets associated with efficacy are summarized in Table 2. Magnitudes of  $fT > MIC$  were higher in the lung model compared with the thigh model, with  $fT > MIC$  of 41.2% versus 29.9% for 1- $\log_{10}$  CFU reduction from baseline and 53.5% versus 38.2% for a 2- $\log_{10}$  CFU reduction from baseline in the lung and thigh models, respectively.

Co-modeling of the durlobactam PK/PD data across multiple MDR isolates and normalizing the  $AUC_{0-24}$  by SUL-DUR MIC in the thigh and lung models resulted in Hill-type model fits shown in Figure 3. The SUL-DUR MIC values of these MDR isolates ranged from 1 to 4  $\mu\text{g}/\text{mL}$ . Correlations ( $r^2$ ) of 0.86 and 0.91 were observed for thigh and lung models, respectively. For studies incorporating a fixed dose of sulbactam (to keep the  $fT > MIC$  of sulbactam consistent throughout the exposure range of durlobactam), a correlation of 0.82 was observed. The magnitudes of durlobactam  $fAUC/MIC$  associated with efficacy are summarized in Table 3. Unbound  $AUC_{0-24}/MIC$  magnitudes were generally consistent in both lung and thigh models as well as in the chemostat model, with  $fAUC_{0-24}/MIC$  magnitudes of 10 and 30 associated with 1- $\log_{10}$  and 2- $\log_{10}$  CFU reductions from baseline, respectively.

## SULBACTAM-DURLOBACTAM PK/PD TARGETS FOR EFFICACY

Taken collectively, the in vitro and in vivo data support a 1- $\log_{10}$  CFU reduction over 24 hours when sulbactam 50%  $fT > MIC$  and durlobactam  $fAUC_{0-24}/MIC$  of 10 in the combination were achieved. This level of bactericidal activity has been suggested to correlate to clinical outcome and efficacy in patients with hospital-acquired pneumonia and bacteremia [34–36].

## CONCLUSIONS

These data confirm  $\%T > MIC$  to be the PK/PD index that best describes sulbactam efficacy, with unbound exposures above the MIC for 50% of the dosing interval being associated with a 1- $\log_{10}$  CFU reduction from baseline based upon data from in vitro dose-fractionation studies. For durlobactam,  $\%T > C_T$  of 0.75  $\mu\text{g}/\text{mL}$  was identified as the PK/PD index associated with efficacy against a single MDR isolate using a one-compartment in vitro infection model. Targeting  $AUC_{0-24}/MIC$  with divided (q6h) dosing, however, was also highly correlated to activity across the MIC range of isolates, with a ratio of approximately 10 being associated with achieving a 1- $\log_{10}$  CFU reduction from baseline when a sulbactam 50%  $fT > MIC$  target associated with this endpoint was also achieved.

Studies completed in vivo also demonstrated that the SUL-DUR combination is effective in treating *A. baumannii*

in neutropenic murine thigh and lung infection models, achieving at least a 1- $\log_{10}$  CFU reduction from baseline over 24 hours of dosing against all MDR isolates evaluated. The magnitudes of the PK/PD indices associated with efficacy for each agent in each of these infection models were relatively consistent between models. An unbound  $AUC:MIC$  ratio of approximately 10 for durlobactam and 50%  $fT > MIC$  for sulbactam for a 1- $\log_{10}$  CFU reduction from baseline were supported by in vivo and in vitro studies and are likely to correlate with clinical efficacy. The results of analyses assessing the probability of attaining these PK/PD targets based on human exposures in the epithelial lining fluid support the proposed clinical dose of 1 g/1 g sulbactam/durlobactam administered via a 3-hour infusion q6h to treat patients with *A. baumannii* isolates with MIC values of 4  $\mu\text{g}/\text{mL}$  or less [37]. Moreover, the most recent in vitro surveillance data demonstrate an SUL-DUR  $MIC_{90}$  of 2  $\mu\text{g}/\text{mL}$  for 5032 ABC isolates, thereby supporting the goal for covering a potentiated MIC of 4  $\mu\text{g}/\text{mL}$  [38]. Based on these results, SUL-DUR may represent a potentially compelling treatment option over current standard of care, which includes high-dose ampicillin-sulbactam administered in combination with tetracyclines, polymyxin B, extended infusions of meropenem, or ceftiderocol [5].

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