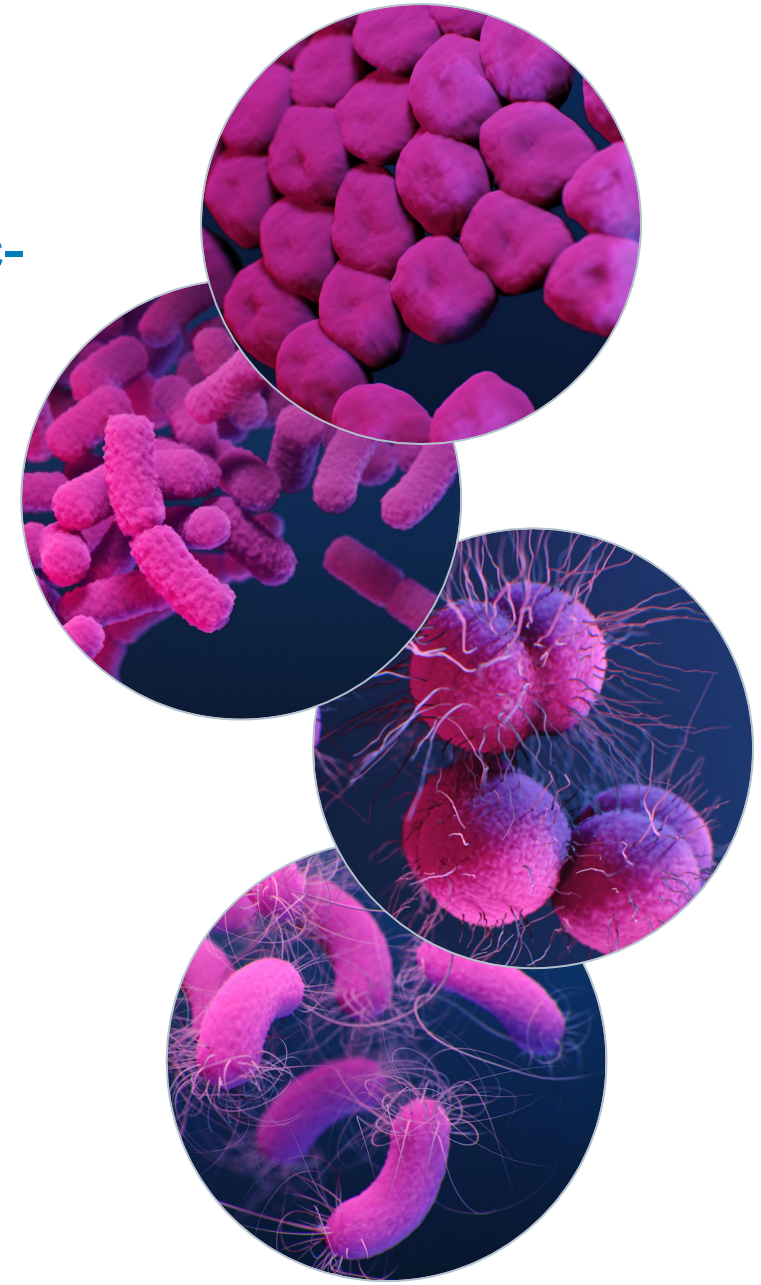
Population Pharmacokinetic, Pharmacokinetic-Pharmacodynamic Attainment, and Clinical Pharmacokinetic-Pharmacodynamic Analyses for Sulbactam-Durlobactam to Support Dose Selection for the Treatment of *Acinetobacter baumannii-calcoaceticus* Complex Infections



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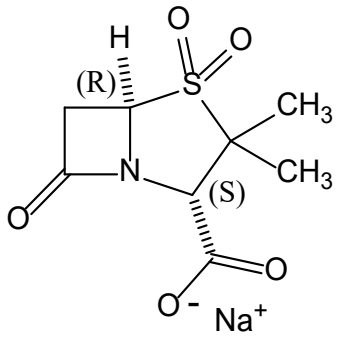
Disclosures

- Sujata M. Bhavnani, Christopher M. Rubino, Jeffrey P. Hammel, Anthony Cammarata, Kathryn Liolios, and Paul G. Ambrose are employees of ICPD which has received research support from Entasis Therapeutics
- Kajal B. Larson, Sarah M. McLeod, Alita A. Miller, and John P. O'Donnell are employees of Entasis Therapeutics
- Rubén Tommasi was an employee of Entasis Therapeutics during the conduct of the analyses

Sulbactam-Durlobactam: A β-Lactam/β-Lactamase Inhibitor Combination in Development for Treatment of *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Infections

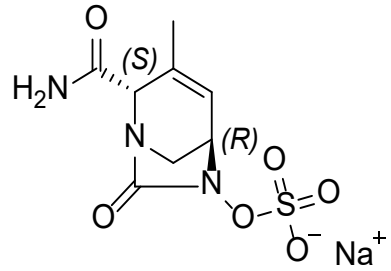
- ABC, identified by the WHO as a priority pathogen for the development of new antibiotics, is a group of closely related *Acinetobacter* species that cause serious infections associated with substantial mortality due to increasing resistance to existing therapies[1]
  - Carbapenem-resistant *A. baumannii* (CRABC) is the fourth leading cause of death attributable to antimicrobial resistance globally[1]
- Sulbactam-durlobactam is a β-lactam/β-lactamase inhibitor combination in development for the treatment of ABC infections

Sulbactam



- Penicillin derivative with intrinsic activity against ABC
- β-lactamase–mediated resistance is common[2] (MIC_{90} value of 64 mg/L; N = 5,032 global clinical isolates)[3]

Durlobactam (ETX2514)



- Diazabicyclooctane β-lactamase inhibitor
- Potent inhibitor of class A, C, and D β-lactamases
- Restores sulbactam activity *in vitro* and *in vivo*

MIC_{90}, minimum inhibitory concentration that inhibits 90% of the microbial strains, WHO, World Health Organization.

1. Antimicrobial Resistance Collaborators. *Lancet.* 2022;399:629-655. 2. Shapiro AB et al. *Front Microbiol*. 2021;12:709974. 3. Karlowsky JA et al. *Antimicrob Agents Chemother*. 2022 Aug 25:e0078122.

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Background

- The clinical development program included the following:
  - 6 Phase 1 studies
  - One Phase 2 study with complicated urinary tract infections (cUTI), including acute pyelonephritis (AP)
  - One Phase 3 study in patients with bacteremia, hospital-acquired bacterial pneumonia (HABP) and ventilator-acquired bacterial pneumonia (VABP)
    - ATTACK was a Phase 3, multinational, randomized, controlled, noninferiority trial conducted to evaluate the efficacy and safety of sulbactam-durlobactam versus colistin, both in combination with imipenem/cilastatin as background therapy, for patients with serious infections due to ABC, including CRABC strains

Objectives

- The following analyses were conducted to support sulbactam-durlobactam dose selection for the treatment of ABC infection
  - Population PK analyses using data from Phase 1, 2, and 3 studies
  - Clinical pharmacokinetic-pharmacodynamic (PK-PD) analyses using data from the Phase 3 ATTACK study
  - PK-PD target attainment analyses using a population PK model, non-clinical PK-PD data, *in vitro* surveillance data, and simulation

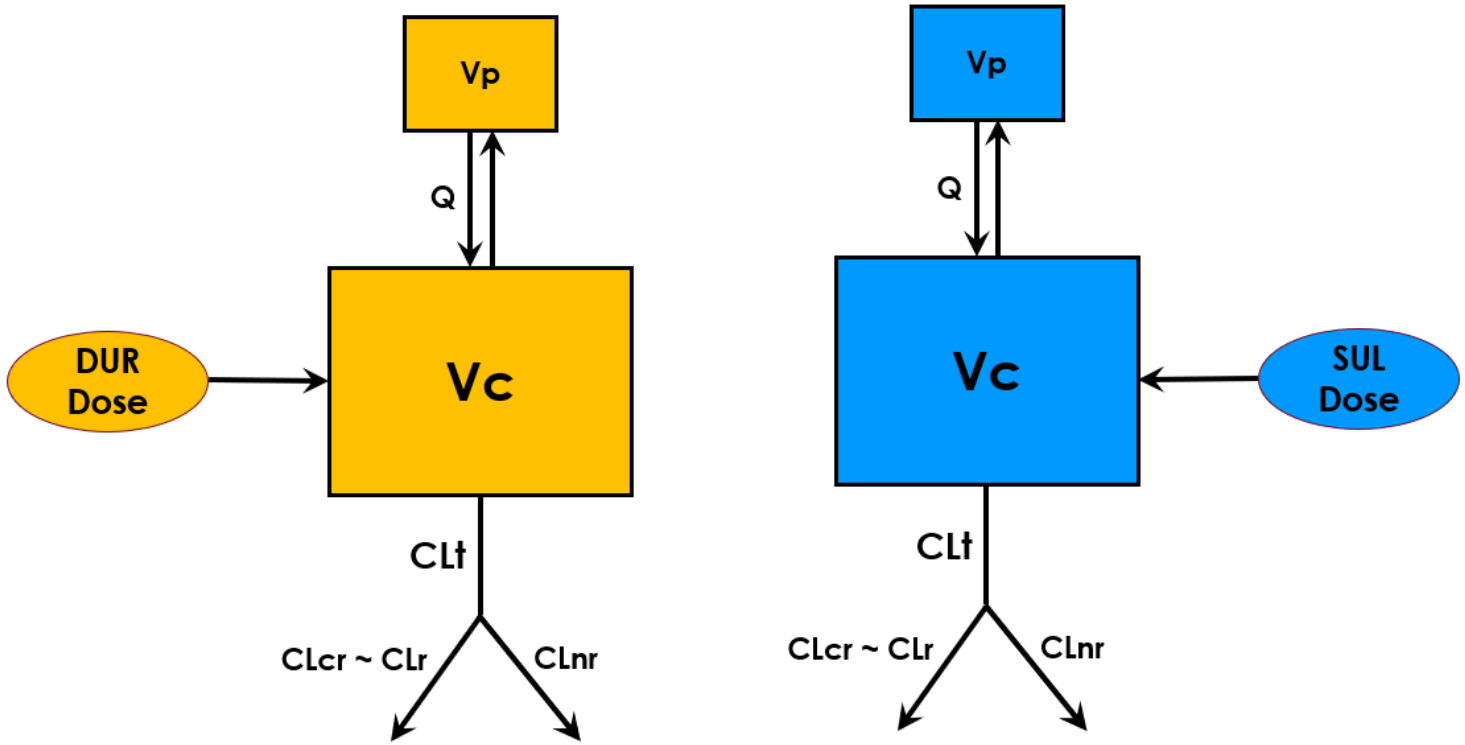
Population PK Analysis Methods

- Previously-developed population PK models[1] were refined using sulbactam and durlobactam available plasma concentration-time data from Phase 1, 2, and 3 clinical studies
- Following construction of the base structural/statistical model for each agent, covariate analyses were conducted to identify subject factors associated with the interindividual variability in PK
  - The relationship between CL and CLcr was included in the population PK model prior to the formal covariate analyses
- Separate models for sulbactam and durlobactam were combined into one consolidated model in which the plasma concentrations of both drugs were fit simultaneously
- Hemodialysis and ELF submodels were developed using data from a Phase 1 renal impairment study[2], and a Phase 1 ELF study[3], respectively

1. Onufrak NJ, *et al*., Population pharmacokinetic and pharmacokinetic-pharmacodynamic target attainment analyses of ETX2514SUL to support dosing regimens in patients with varying renal function. ECCMID; April 13-6, 2019; Amsterdam, NL. Poster #P1953.
2. O'Donnell JP, *et al*., Pharmacokinetics, safety, and tolerability of intravenous durlobactam and sulbactam in subjects with renal impairment and healthy matched control subjects. Antimicrob Agents Chemother; 2019; 63(9):e00794-19.
3. Rodvold KA, *et al*., Plasma and intrapulmonary concentrations of ETX2514 and sulbactam following intravenous administration of ETX2514SUL to healthy adult subjects. Antimicrob Agents Chemother; 2018; 62(11):e01089-18.

Population PK Analysis Results

Schematic representation of the base structural models for durlobactam and sulbactam



Abbreviations: CLcr = creatinine clearance; CLnr = nonrenal clearance from plasma; CLr = renal clearance from plasma; CLt = total clearance; DUR = durlobactam, Q = distributional clearance; SUL = sulbactam; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment.

- The dataset contained 5,390 plasma concentrations from 211 subjects from six Phase 1 studies and 162 patients from Phase 2 and 3 studies
- A four-compartment model, with two compartments for each of sulbactam and durlobactam, with first-order, linear elimination best characterized the time-course of sulbactam and durlobactam
- Hemodialysis and ELF submodels
  - Hemodialysis submodels showed that CL of both sulbactam and durlobactam were increased during hemodialysis
  - ELF penetration relative to total-drug concentrations for durlobactam and sulbactam was 37.2 and 53.3%, respectively

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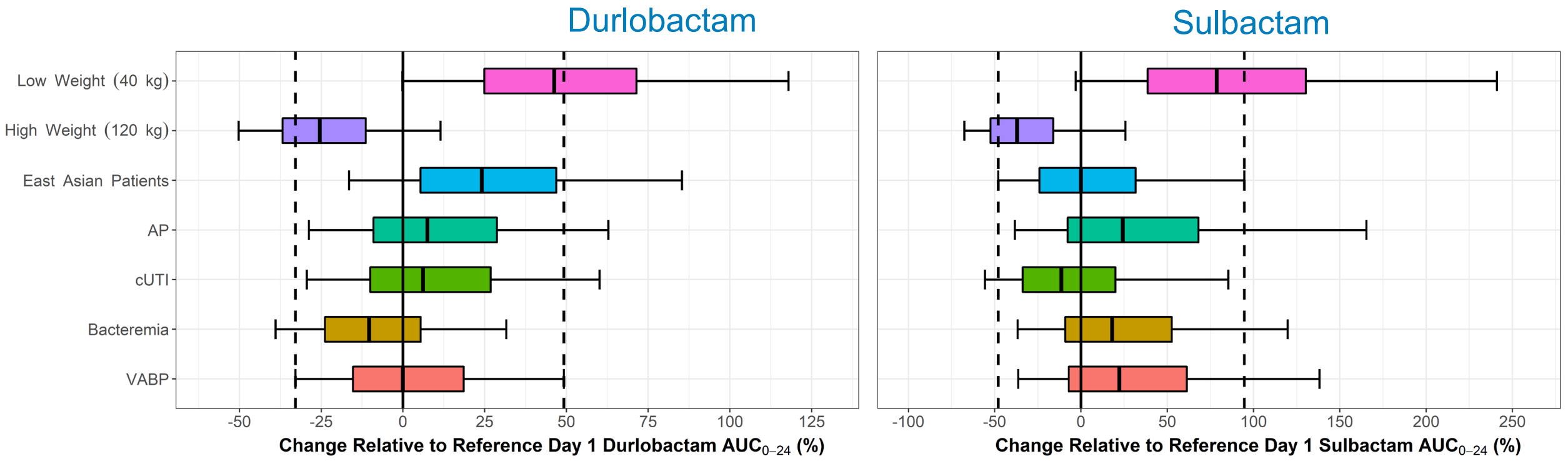
Population PK Analysis Results



Reference Population: CLCRN=100 (mL/min/1.73m^2), WTKG=75 kg, Not East Asian, and Infected (HABP)

Dashed lines and whiskers represent 5th and 95th percentiles

- Body weight, site of infection, and East Asian region (which grouped patients from mainland China, Taiwan, and South Korea vs others) were found to be statistically significant covariates in the population PK analysis but were not clinically relevant
- Renal function was a statistically and clinically relevant covariate in the model, and dose adjustments are needed based on renal function

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Clinical PK-PD Analyses for Efficacy Methods

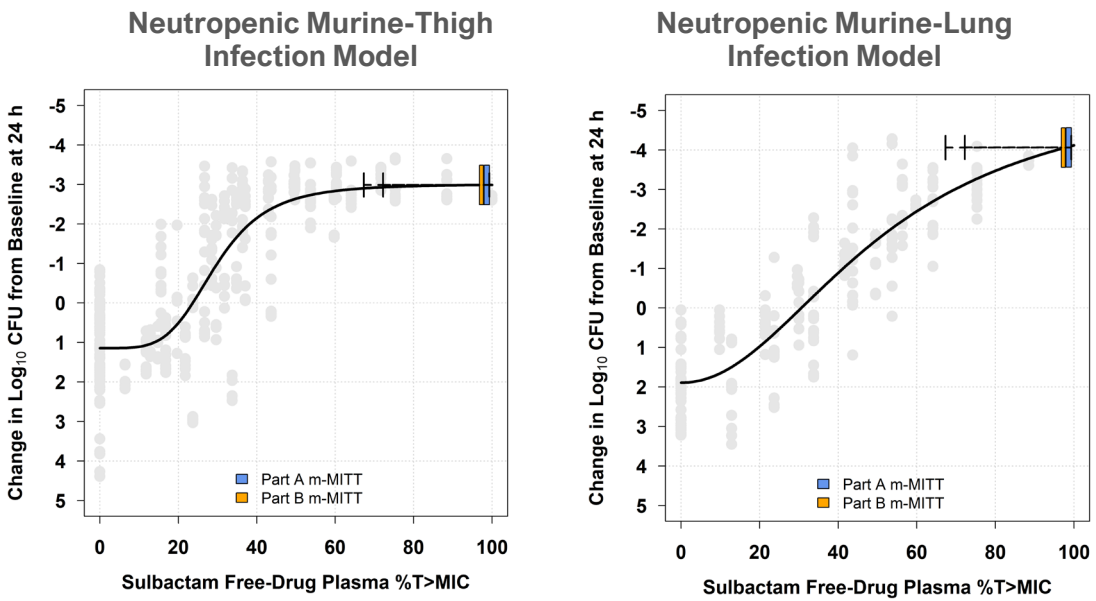
- Clinical PK-PD relationships were assessed using dichotomous and time-to-event efficacy endpoints and data from the Phase 3 ATTACK study
  - Dichotomous efficacy endpoints: 14- and 28-day all-cause mortality, and both clinical and microbiological response at End of Treatment, Test of Cure, and Late Follow-Up
  - Time-to-event efficacy endpoint: Time to all-cause mortality, which was assessed over 28 days
- PK-PD indices for sulbactam and durlobactam in the form of continuous and categorical variables were assessed for associations with the dichotomous and time to all-cause mortality endpoints using logistic regression and Cox proportional hazards regression, respectively
  - Free-drug plasma and total-drug ELF sulbactam %T>MIC and durlobactam AUC:MIC ratio on Days 1, 1 to 2, and 1 to 3 were considered individually and jointly with respect to their associations with each efficacy endpoint

Results Clinical PK-PD Analyses

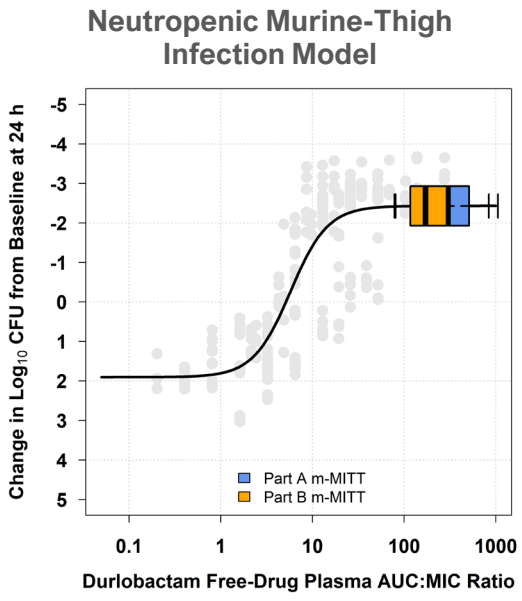
- Results of the clinical PK-PD analyses for efficacy based on data from the Phase 3 ATTACK study did not suggest relationships between efficacy endpoints and sulbactam and/or durlobactam PK-PD indices
  - Only a small fraction of the univariable analyses performed yielded statistically significant PK-PD relationships for sulbactam or durlobactam PK-PD indices
  - The totality of the findings demonstrated a general absence of statistically significant relationships at individual 0.10 levels, with exceptions occurring less frequently than the expectation by chance alone

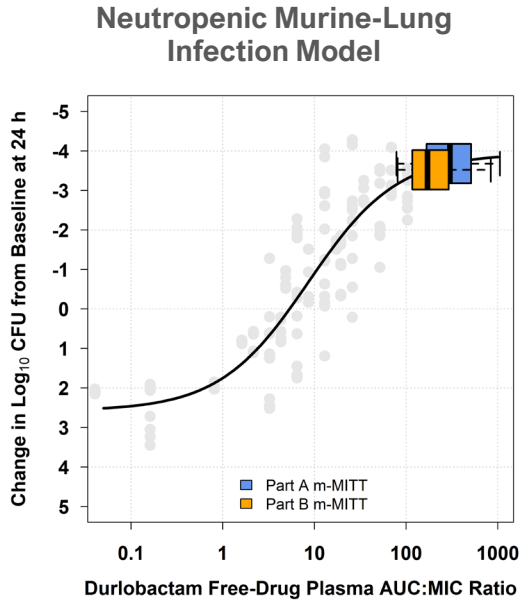
Non-Clinical PK-PD Relationships for *A. baumannii* Efficacy, Overlaid with PK-PD Indices for Patients from the Phase 3 ATTACK Study

Sulbactam



Durlobactam





Horizontal box-and-whisker plots of the sulbactam free-drug plasma %T>MIC over Days 1 to 3 and the average of Days 1 to 3 durlobactam free-drug plasma AUC:MIC ratio among patients in the Part A and Part B m-MITT Analysis Populations after administration of sulbactam 1 g/ durlobactam 1 g IV q6h or dosing regimens adjusted for renal function are shown overlaid on PK-PD relationships for *A. baumannii* efficacy based on data from neutropenic murine-thigh and -lung infection models. For each boxplot, the vertical edge of the box represents the 25th to the 75th percentiles of the distribution for sulbactam free-drug plasma %T>MIC. The vertical line within the box represents with median sulbactam free-drug plasma %T>MIC or durlobactam free-drug plasma AUC:MIC ratio. The whiskers extend to the 5th and 95th percentiles.

- All or a large majority of patients achieved PK-PD indices that were above non-clinical PK-PD targets associated with 1- and 2-$\log_{10}$ CFU reductions from baseline and which were on the upper plateau of non-clinical PK-PD relationships (i.e., ≥ 2-$\log_{10}$ CFU reduction from baseline)

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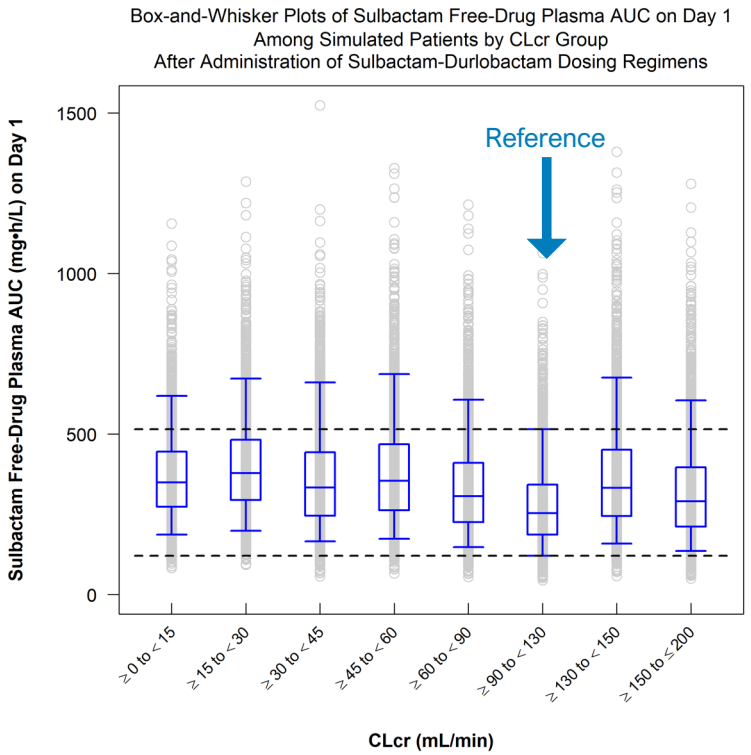
PK-PD Target Attainment Analysis Methods

- Summaries of drug exposures and percent probabilities of PK-PD target attainment by MIC were assessed in simulated patients with ABC infections by CLcr group
- Assessments were based on free-drug plasma and total-drug ELF exposures in simulated patients and free-drug plasma targets associated with a 1-$\log_{10}$ CFU reduction from baseline
  - PK-PD targets from neutropenic murine-thigh and -lung infection models: sulbactam free-drug plasma %T>MIC target ≥ 50% with durlobactam free-drug plasma AUC:MIC ratio target ≥ 10
  - Since total-drug ELF targets from neutropenic murine-lung infection models were not available, free-drug plasma PK-PD targets were assessed relative to total-drug ELF exposures in simulated patients
- *In vitro* surveillance data for 7,026 *Acinetobacter* isolates collected from relevant geographic areas worldwide over a period between 2013 and 2020 were used to interpret the findings of the PK-PD target attainment analyses

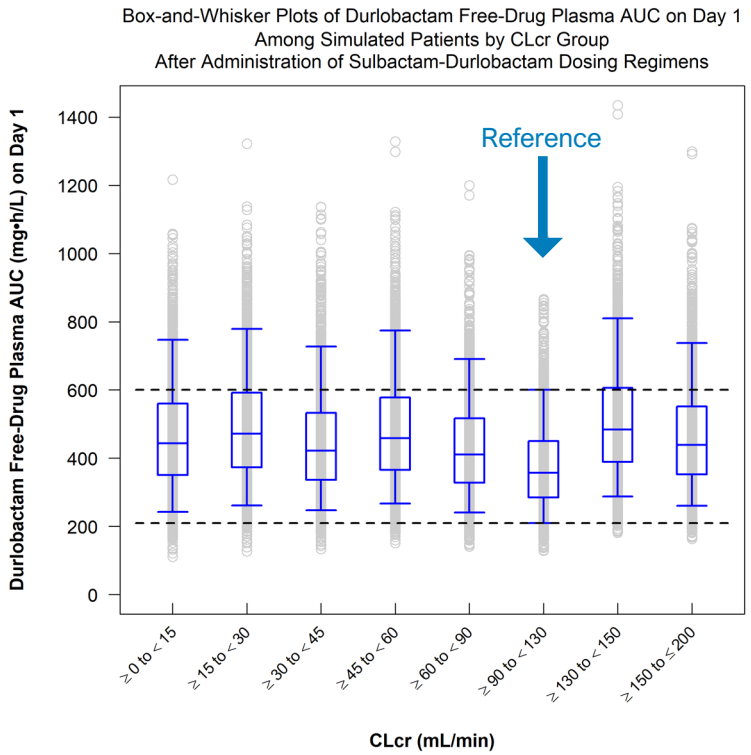
Evaluation of Sulbactam-Durlobactam Dosing Regimens Adjusted for Renal Function

- Sulbactam-durlobactam dosing regimens adjusted for renal function group were selected based on the percentage of simulated patients with Day 1 and 3 AUC values inside the 90% prediction interval of simulated patients with normal renal function (CLcr > 90 to ≤ 130 mL/min) after administration of sulbactam 1 g/ durlobactam 1 g q6h

Sulbactam



Durlobactam



Selected sulbactam-durlobactam dosing regimens based on baseline CLcr

Baseline CLcr (mL/min)	Sulbactam/ Durlobactam dose	Dose interval
≥ 150 to ≤ 200	1.5 g/1.5 g IV	q6h
≥ 130 to < 150		
≥ 90 to < 130	1 g/1 g IV	
≥ 60 to < 90		
≥ 45 to < 60		
≥ 30 to < 45		q8h
≥ 15 to < 30	1 g/1 g IV loading dose followed by 0.5 g/0.5 g IV	q8h
≥ 0 to < 15	1 g/1 g IV loading dose followed by 0.5 g/0.5 g IV	q12h

Abbreviations: AUC = area under the concentration time curve; CL_{CR} = creatinine clearance.
The horizontal dashed lines represent the 90% prediction interval of the ≥ 90 to < 130 mL/min group, which is defined as the 5th and 95th percentiles for sulbactam or durlobactam free-drug plasma AUC on Days 1

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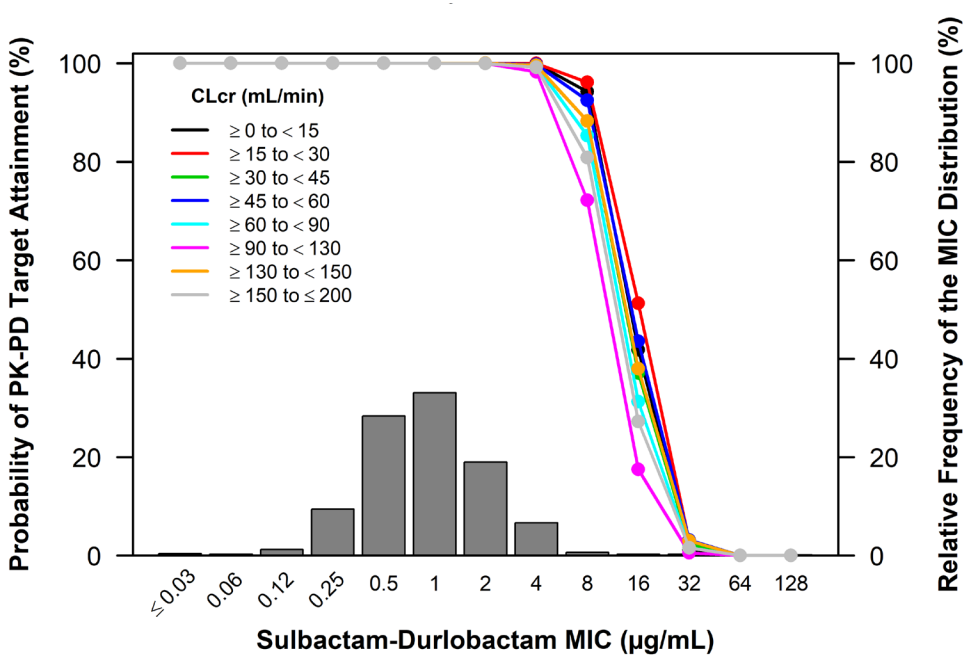
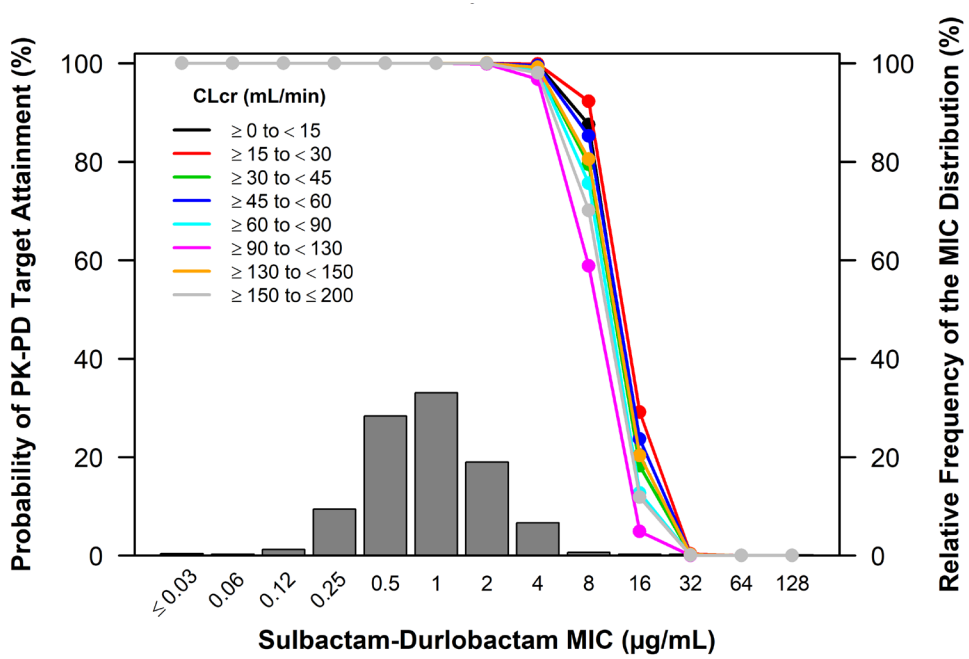
PK-PD Target Attainment Analysis Results

Assessment of Free-Drug Plasma Exposures



Assessment of Total-Drug ELF Exposures



- Percent probabilities of PK-PD target attainment based on free-drug plasma and total-drug ELF exposures and PK-PD targets associated with a 1-$\log_{10}$ CFU reduction from baseline were ≥ 90% for pathogens with an MIC ≤ 4 µg/mL (i.e., the MIC value inhibiting 98.4% of the collection of ABC isolates) among simulated patients across renal function categories

The distribution of sulbactam-durlobactam MIC values presented for 7,026 *Acinetobacter* isolates were tested using a fixed durlobactam concentration of 4 ug/mL in the presence of sulbactam.

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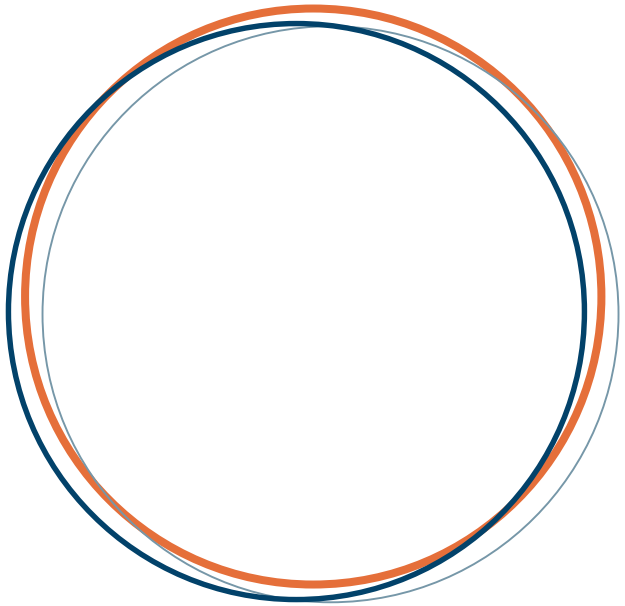
Conclusions

- Final plasma population PK model and submodels for ELF for sulbactam and durlobactam described the PK data well and were considered appropriate for generating individual post-hoc estimates for conducting the PK-PD analyses and model-based simulations
- Results of the clinical PK-PD analyses for efficacy based on data from the Phase 3 ATTACK study did not suggest relationships between efficacy endpoints and sulbactam and/or durlobactam PK-PD indices
  - This finding was consistent with patients with PK/PD indices that were on the plateau of potential clinical PK/PD relationships for efficacy and with most patients achieving sulbactam-durlobactam exposures that were above non-clinical PK/PD targets for efficacy
- The results of PK-PD target attainment analyses based on both plasma and ELF exposures support the use of sulbactam 1 g/ durlobactam 1 g IV q6h in patients with infections caused by ABC and provided guidance for dosing regimens adjusted for renal function
- These data support a proposed susceptible MIC breakpoint of 4 µg/mL for sulbactam-durlobactam against *Acinetobacter* spp.



Thank you!

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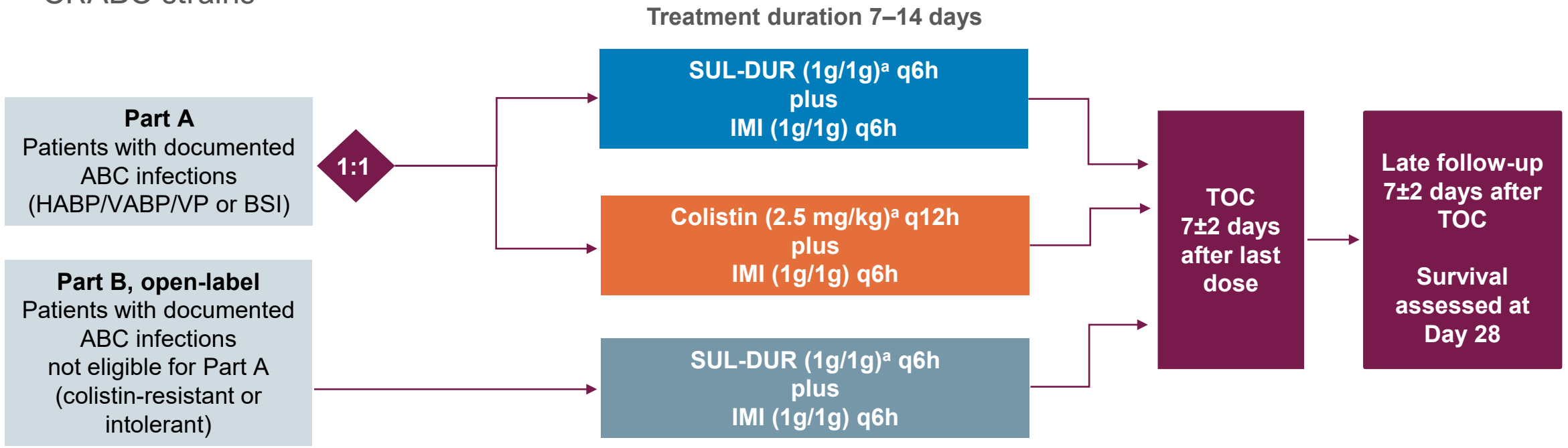
ATTACK Study Design

- ATTACK was a Phase 3, multinational, randomised, controlled, noninferiority trial conducted to evaluate the efficacy and safety of sulbactam-durlobactam versus colistin, both in combination with imipenem/cilastatin as background therapy, for patients with serious infections due to ABC, including CRABC strains



This trial was registered at ClinicalTrials.gov: NCT03894046 [ECCMID abstract #02060, Altarac *et al*. *Efficacy and safety of sulbactam-durlobactam (SUL-DUR) versus colistin therapy in patients with Acinetobacter baumannii-calcoaceticus complex (ABC) infections: a global, randomised, active-controlled Phase 3 trial (ATTACK* for Part A. ECCMID abstract #02093, Altarac *et al*. *Efficacy and safety of sulbactam-durlobactam (SUL-DUR) therapy in patients with Acinetobacter baumannii-calcoaceticus complex (ABC) infections in the open-label Part B of the ATTACK Phase 3 trial* for Part B].

a. Sulbactam-durlobactam (SUL-DUR) dosing was adjusted for renal function. Colistin dosing was adjusted to ideal body weight and renal function. A single colistin loading dose of 2.5 to 5 mg/kg given intravenously over 3 to 6 minutes (or according to standard of care) was administered on Day 1 for patients who had not received prior colistin therapy. BSI, bloodstream infection; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem/cilastatin; q6h, every 6 hours; q12h, every 12 hours, TOC, test of cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia.

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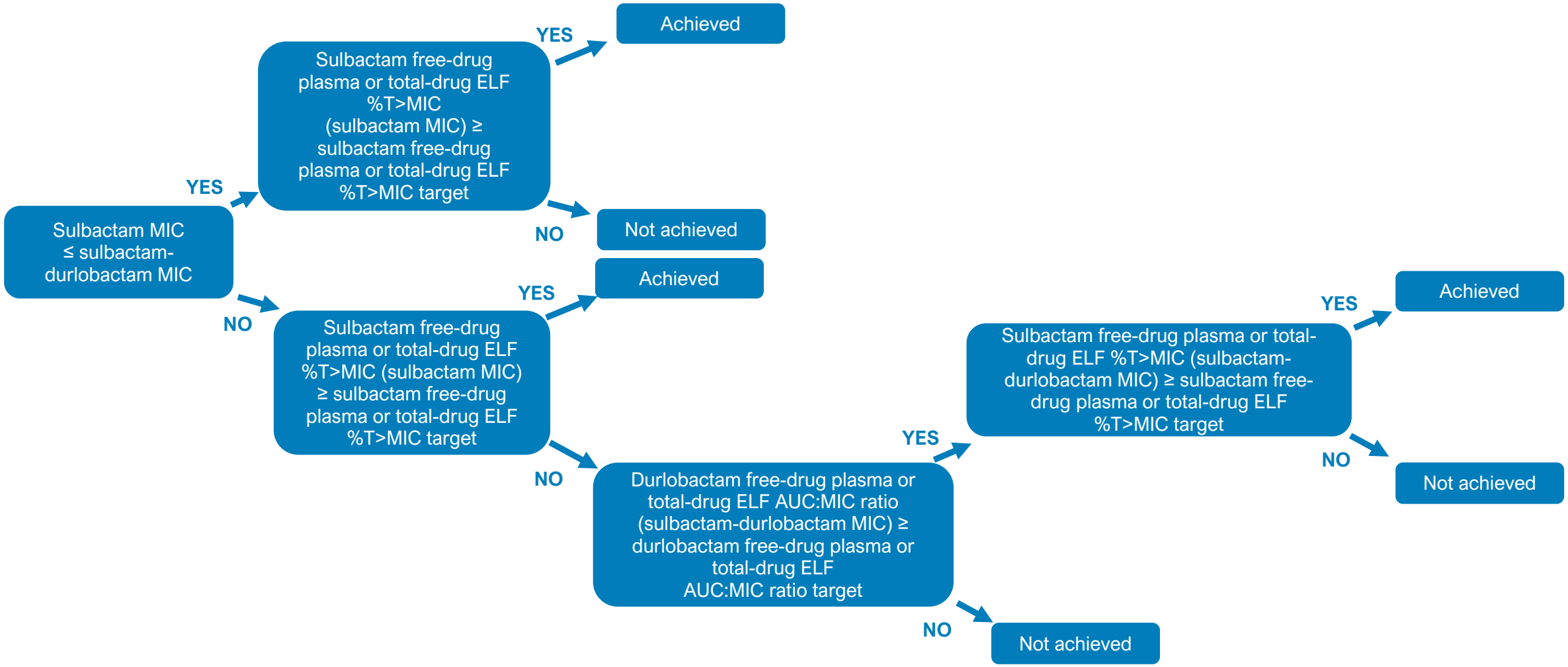
Algorithm to Calculate Percent Probabilities of PK-PD Target Attainment



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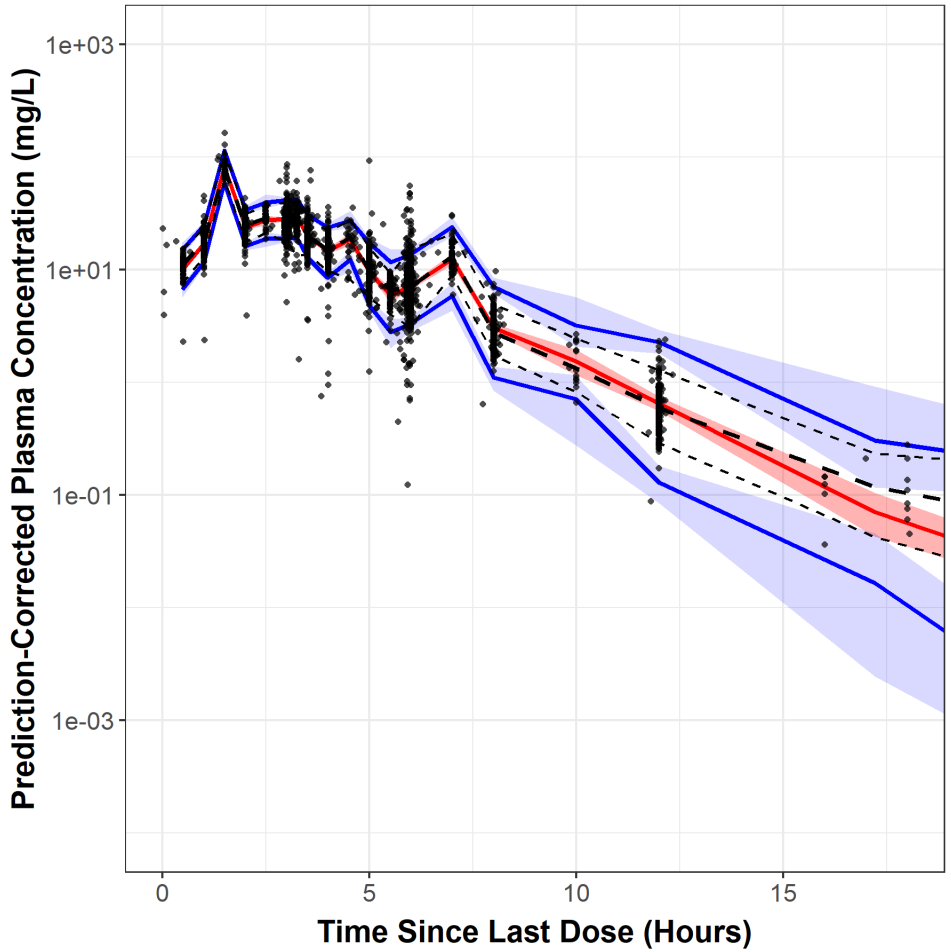
Predicted-Corrected Visual Predicted Checks

Prediction-corrected visual predictive check plot for the final model using the pooled analysis dataset and durlobactam concentrations



Circles are observed concentrations, the black long dashed lines are the median observed concentrations, black short dashed lines are the 5th and 95th percentiles of the observed concentrations. The solid red line represents the median model predicted concentration values. The solid blue lines represent the 5th and 95th model predicted concentration values. Shaded areas represent the 90% prediction interval around the 5th, median, and 95th model predictions.

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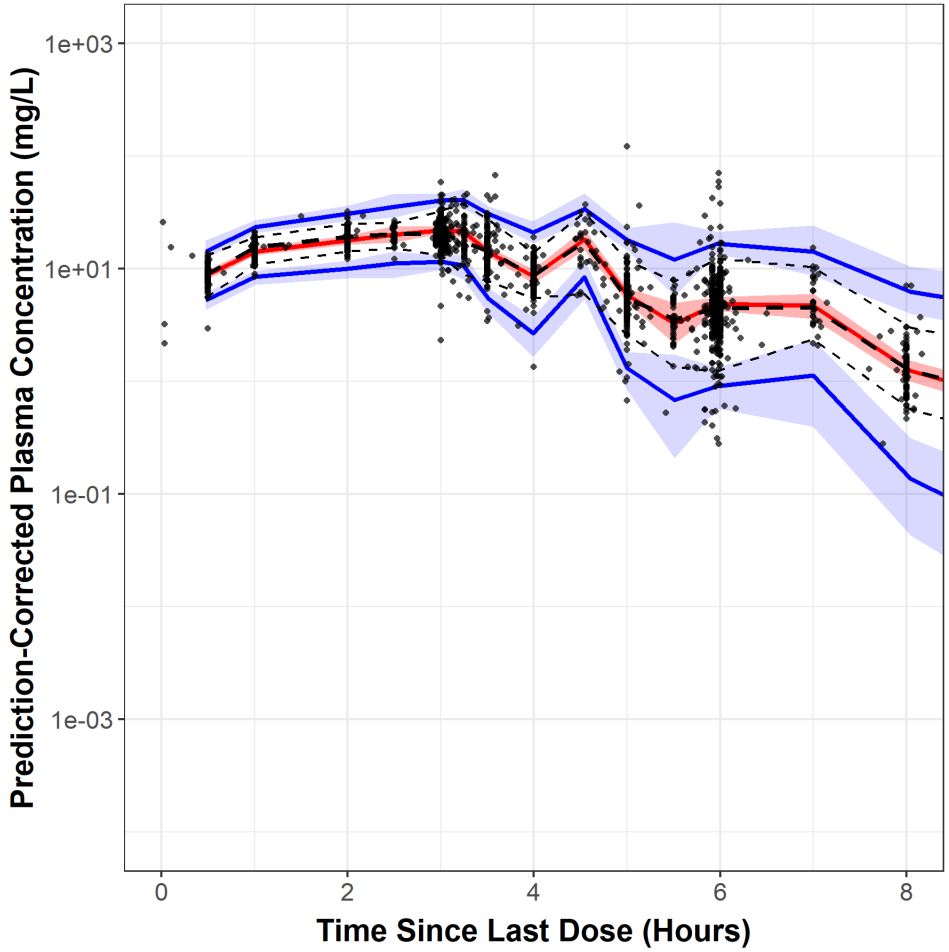
Predicted-Corrected Visual Predicted Checks

Prediction-corrected visual predictive check plot for the final model using the pooled analysis dataset and sulbactam concentrations



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