

Poster P-444

Population pharmacokinetics analysis of sulbactam-durlobactam to support the dose selection for evaluation in a clinical trial in pediatric patients with *Acinetobacter baumannii-calcoaceticus* complex infections

Anthony Cammarata¹, Kajal B. Larson², Angela Tanudra², John P. O'Donnell^{2*}, Sujata M. Bhavnani¹, and Chris M. Rubino¹

¹Institute of Clinical Pharmacodynamics, Schenectady, NY, USA; ²Innoviva Specialty Therapeutics, Inc. an affiliate of Entasis Therapeutics Inc., Waltham, MA ,USA

*Current affiliation Aurobac Therapeutics, Lyon, France

Innoviva Specialty Therapeutics, Inc.
930 Winter Street Suite 1500
Waltham, MA 02451
Kajal.Larson@istx.com

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Background

Sulbactam-durlobactam (SUD) is a combination β-lactam/β-lactamase inhibitor that has been approved in the United States for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* complex (ABC) in patients aged 18 years and older [1].

The pharmacokinetics (PK) of sulbactam, durlobactam, and their combination have been studied in adults in six Phase 1 trials, one Phase 2 trial, and one Phase 3 trial. Currently, no clinical trial data are available for pediatric patients.

A Phase 1b clinical trial (NCT06801223) evaluating the PK, safety, and tolerability of SUD in pediatric patients (birth to < 18 years of age) with ABC infection is underway. The dosing regimens for the pediatric trial were selected based on the nonclinical data, adult clinical data, and pharmacometric analyses. The population PK analyses are described herein.

Methods

The adult population PK model of SUD was based on a dataset containing 8,100 plasma concentrations from 432 adult subjects [2]. The combined model was a four-compartment (two compartments per drug) model with linear kinetics (**Figure 1**). Both renal clearance and nonrenal clearance were estimated, and total clearance was calculated as the sum of renal and nonrenal clearance. Individual renal clearances were scaled by baseline creatinine clearance (CL_{CR}).

To determine pediatric SUD dosing, two distinct modeling approaches were utilized - Adult with Allometry and Allometry + CL_{CR}:

- The first approach utilized the full covariate model from adults with the only change being the use of allometric scaling with fixed exponents of 0.75 for clearance and 1.0 for volume of distribution
- The second approach removed all covariate relationships from the Adult Allometry model except for body weight (on all parameters) and renal function (on renal clearance only)

Adult Allometry Population PK Model	Adult Allometry + CL _{CR} Population PK Model
$CL_{NR_DUR} = (1 - 0.660) \times 9.36$ $CL_{R_DUR} = 0.660 \times 9.36 \times \left[\frac{CL_{CR}}{90} \right]^{0.694}$ $CL_{intDUR} = (CL_{intRena} + CL_{intRen}) \times \left[\frac{WT^{0.75}}{75} \right] \times (1 - 0.508 \times BCLCRNL30) \times (1 - 0.191 \times EASIAFL)$ $V_{Cint} = 12.5 \times \left[\frac{WT^{1.00}}{75} \right] \times (1 - 0.261 \times EASIAFL) \times (1 + \Theta_{int}(V_{CintFPN}))$ $Q_{DUR} = 4.42 \times \left[\frac{WT^{0.75}}{75} \right]$ $V_{Pint} = 5.83 \times \left[\frac{WT^{1.00}}{75} \right]$ Durlobactam	$CL_{NR_DUR} = (1 - 0.660) \times 9.36 \times \left[\frac{WT^{0.75}}{75} \right]$ $CL_{R_DUR} = 0.660 \times 9.36 \times \left[\frac{CL_{CR}}{90} \right]^{0.694}$ $CL_{intDUR} = (CL_{intRena} + CL_{intRen}) \times \left[\frac{WT^{0.75}}{75} \right] \times (1 - 0.508 \times BCLCRNL30) \times (1 + \Theta_{int}(V_{CintFPN}))$ $V_{Cint} = 12.5 \times \left[\frac{WT^{1.00}}{75} \right]$ $Q_{DUR} = 4.42 \times \left[\frac{WT^{0.75}}{75} \right]$ $V_{Pint} = 5.83 \times \left[\frac{WT^{1.00}}{75} \right]$ Durlobactam
$CL_{NR_SUL} = (1 - 0.648) \times 13.6$ $CL_{R_SUL} = 0.648 \times 13.6 \times \left[\frac{CL_{CR}}{90} \right]^{0.932}$ $CL_{intSUL} = (CL_{intRena} + CL_{intRen}) \times \left[\frac{WT^{0.75}}{75} \right] \times (1 - 0.560 \times BCLCRNL30) \times (1 + \Theta_{int}(V_{CintFPN}))$ $V_{Cint} = 12.1 \times \left[\frac{WT^{1.00}}{75} \right] \times (1 + \Theta_{int}(V_{CintFPN}))$ $Q_{SUL} = 7.82 \times \left[\frac{WT^{0.75}}{75} \right]$ $V_{Pint} = 6.98 \times \left[\frac{WT^{1.00}}{75} \right]$ Sulbactam	$CL_{NR_SUL} = (1 - 0.648) \times 13.6 \times \left[\frac{WT^{0.75}}{75} \right]$ $CL_{R_SUL} = 0.648 \times 13.6 \times \left[\frac{CL_{CR}}{90} \right]^{0.932}$ $CL_{intSUL} = (CL_{intRena} + CL_{intRen}) \times \left[\frac{WT^{1.03}}{75} \right] \times (1 + \Theta_{int}(V_{CintFPN}))$ $V_{Cint} = 12.1 \times \left[\frac{WT^{1.00}}{75} \right]$ $Q_{SUL} = 7.82 \times \left[\frac{WT^{0.75}}{75} \right]$ $V_{Pint} = 6.98 \times \left[\frac{WT^{1.00}}{75} \right]$ Sulbactam

- Notes:
- CL_{CR} represents GFR normalized to BSA in units of mL/min/1.73m²
 - Infection type was set to "Bacteremia"
 - East Asian flag was set to "not East Asian"
 - WTKG effects added to Q and V_p for both drugs to account for likely changes in these parameters in children

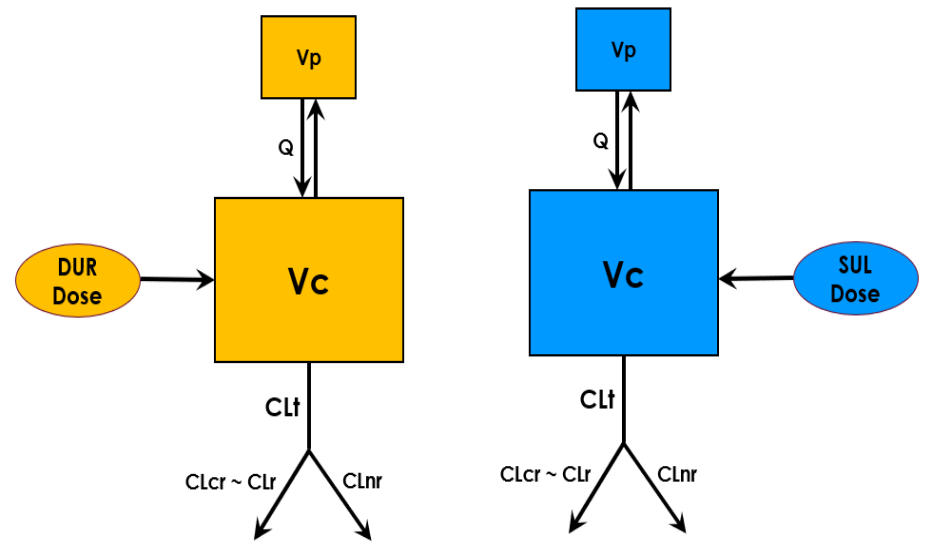
A simulated dataset of 8,000 hypothetical pediatric patients (1,000 per Cohort, **Table 1**) was generated, incorporating age- and sex-specific body size distributions based on the published Centers for Disease Control and Prevention (CDC) growth chart for height and weight [3] and assuming normal renal function

Monte Carlo simulations were conducted to generate concentration-time profiles for each hypothetical individual and predicted exposures were compared to those observed in adults during Phase 2 and 3 studies

Probability of pharmacokinetic/pharmacodynamic (PK/PD) target attainment (PTA) was also predicted based on the respective PK/PD drivers:

- Sulbactam: %fT>MIC of > 50%
- Durlobactam: fAUC/MIC ratio of 10

Figure 1 : Final adult four-compartment model with linear kinetics



Abbreviations: CL_{CR}, creatinine clearance; CL_{nr}, Non-renal clearance; CL_r, renal clearance; CL_t, total clearance; DUR, durlobactam; SUL, sulbactam; V_c, Volume of distribution of the central compartment; V_p, Volume of distribution of the peripheral compartment; Q, distributional clearance

Results

The adult SUD exposures on Day 1 and Day 3 are shown in **Table 1** and demonstrate lack of accumulation SUD exposures and PTA using each model are shown in **Figures 2** and **3** and guided the selection of dosing regimens shown in **Table 2**:

- The adult with allometry model provided SUD exposures that were predominantly contained within the 5th and 95th percentiles of adult exposures based on AUC₀₋₂₄
- Compared to the adult with allometry model, the adult with allometry + CL_{CR} model predicted lower SUD exposures, which would have supported the selection of higher doses
- Thus, the adult with allometry model represents a more conservative approach for initial dose selection for the pediatric clinical trial

Safety and PK data will be evaluated throughout the trial to ensure that the dosing regimens are appropriate

Table 1: Median (5th - 95th percentile) Adult Sulbactam and Durlobactam Exposures

Drug	PK Parameter	Day 1	Day 3
Sulbactam	AUC ₀₋₂₄ (h·µg/mL)	441 (196—1170)	469 (192—1710)
	C _{max} (µg/mL)	30.0 (14.7—75.9)	29.5 (14.3—88.8)
Durlobactam	AUC ₀₋₂₄ (h·µg/mL)	442 (277—904)	479 (239—1180)
	C _{max} (µg/mL)	30.3 (18.4—58.9)	30.5 (17.3—65.0)

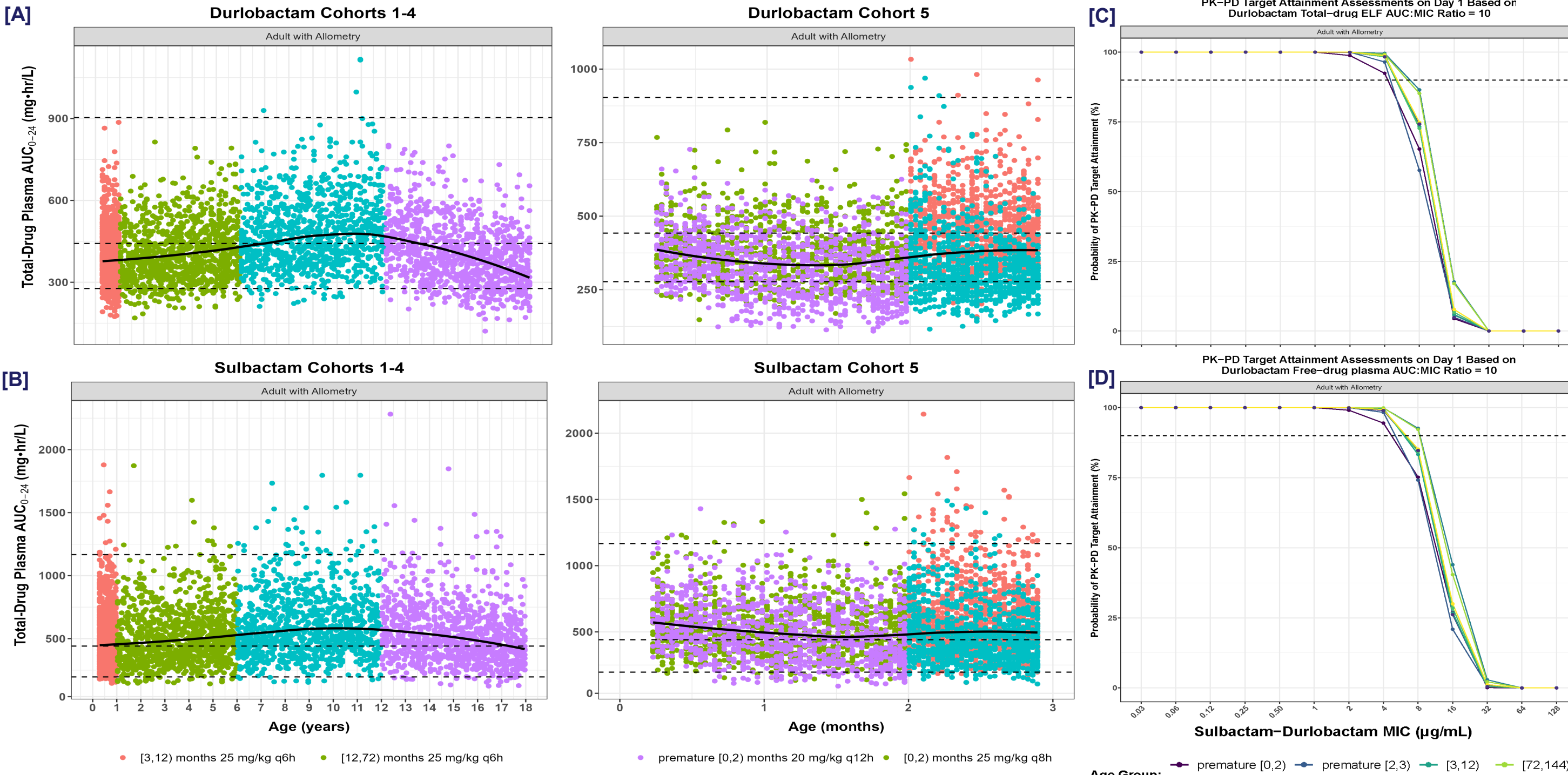
Abbreviations: AUC₀₋₂₄ = area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} = maximum plasma concentration; PK = pharmacokinetic

Table 2. Pediatric SUD Dosing Regimens by Age Cohort (3-hour IV infusion) for Evaluation in the Phase 1b Pediatric Trial

Cohort	Age range	Dosage Regimen to be Evaluated
Cohort 1	12 to < 18 y	25 mg/kg SUL and 25 mg/kg DUR[a], q6h
Cohort 2	6 to < 12 y	25 mg/kg SUL and 25 mg/kg DUR[a], q6h
Cohort 3	1 to < 6 y	25 mg/kg SUL and 25 mg/kg DUR, q6h
Cohort 4	3 mo to < 1 y	25 mg/kg SUL and 25 mg/kg DUR, q6h
Cohort 5, Subgroup 1		
Term	2 to < 3 mo	25 mg/kg SUL and 25 mg/kg DUR, q6h
Preterm	2 to < 3 mo	20 mg/kg SUL and 20 mg/kg DUR, q8h
Cohort 5, Subgroup 1		
Term	Birth to <2 mo	25 mg/kg SUL and 25 mg/kg DUR, q8h
Preterm	Birth to <2 mo	20 mg/kg SUL and 20 mg/kg DUR, q12h

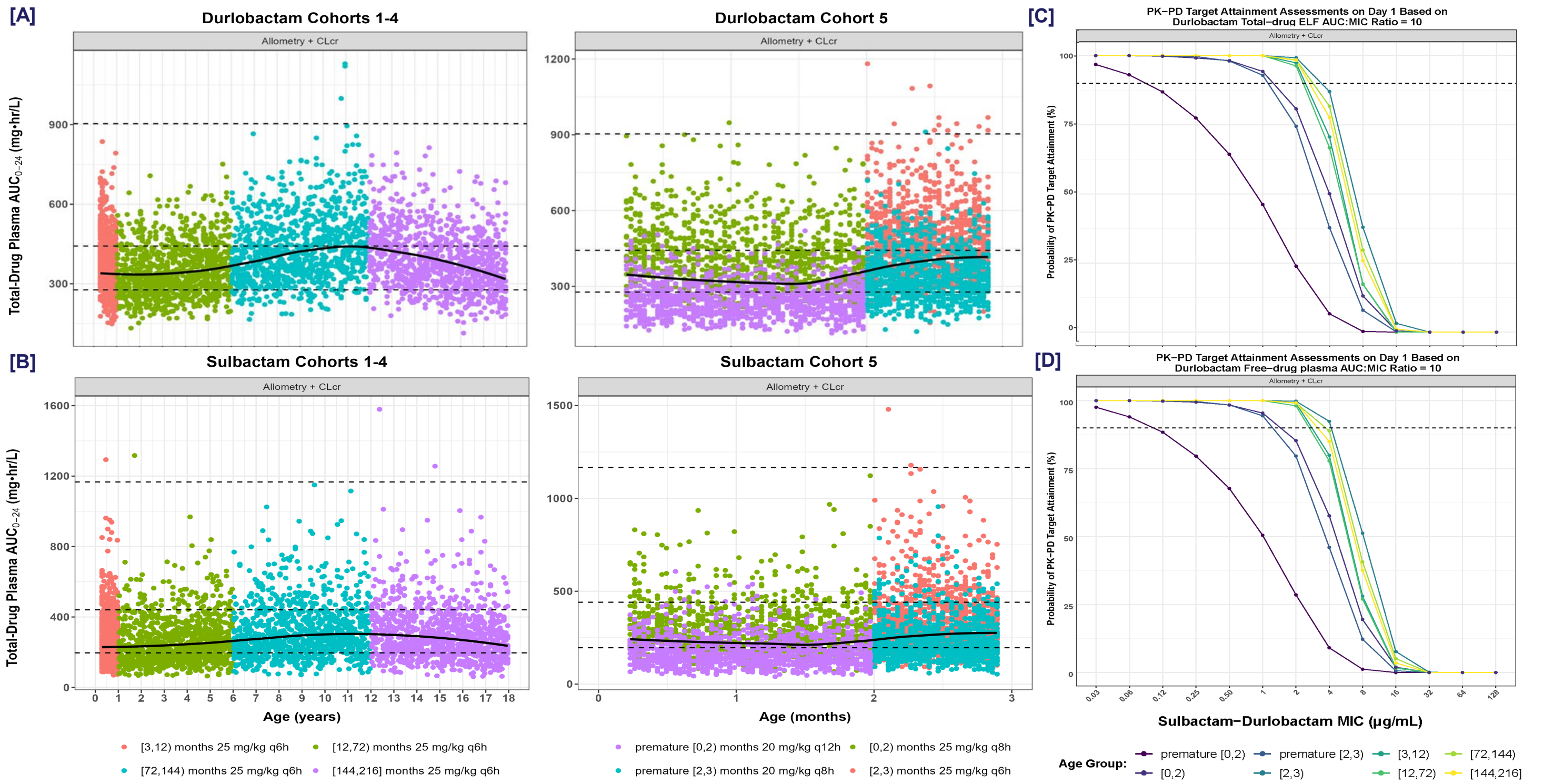
Abbreviations: DUR, durlobactam; IV, intravenous; qhx, every x hours; SUL, sulbactam
[a] Not to exceed a total dose of 1 g SUL and 1 g DUR
Notes: The doses above may be modified based on evaluation of PK and safety data from clinical trial NCT06801223; The ratio of sulbactam-durlobactam is 1:1, administered via a 3-hour IV infusion. Birth is defined 7 days post-natal.

Figure 2. Adult with Allometry Model: **[A]** Durlobactam and **[B]** Sulbactam total-drug plasma AUC₀₋₂₄ on Day 1 by age, compared to adult Phase 2/3 post-hoc estimates; PK/PD target attainment assessment on Day 1 based on Durlobactam **[C]** total-drug ELF and **[D]** free-drug plasma AUC/MIC ratio of 10, with a Sulbactam target of 50% fT>MIC



Abbreviations: 50% fT>MIC, 50 % of time that free concentrations are above the MIC; AUC₀₋₂₄, area under the plasma concentration-time curve from time 0 to 24 hours; ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PD, pharmacodynamic; qhx, every x hours. Solid black line shows median exposure by age; dashed lines indicate 5th, median, and 95th percentiles from the adult Phase 2/3 studies; PTA dashed line marks the 90% PTA

Figure 3. Adult Allometry + CL_{CR} Model : **[A]** Durlobactam and **[B]** Sulbactam total-drug plasma AUC₀₋₂₄ on Day 1 by age, compared to adult Phase 2/3 post-hoc estimates; PK/PD Target attainment assessment on Day 1 based on Durlobactam **[C]** total-drug ELF and **[D]** free-drug plasma AUC/MIC ratio of 10, with a Sulbactam target of 50% fT>MIC



Abbreviations: 50% fT>MIC, 50 % of time that free concentrations are above the MIC; AUC₀₋₂₄, area under the plasma concentration-time curve from time 0 to 24 hours; ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PD, pharmacodynamic; qhx, every x hours. Solid black line shows median exposure by age; dashed lines indicate 5th, median, and 95th percentiles from the adult Phase 2/3 studies; PTA dashed line marks the 90% PTA

Conclusions

- Two models (Adult with Allometry and Allometry + CL_{CR}) were explored to select doses for the first SUD pediatric trial
- Monte Carlo simulations were conducted to determine dosing regimens that are predicted to yield safe and efficacious SUD exposures
- The adult SUD population PK model, modified to incorporate allometric scaling, was used to predict SUD exposures in pediatric patients as it provides a more conservative initial dose estimate
- These pediatric SUD dosing regimens are being evaluated in a Phase 1b clinical trial (NCT06801223); interim analyses will be conducted to ensure that the dosing regimens are appropriate
- The most appropriate model will be evaluated once pediatric data are available

References

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