### Title

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# Population Pharmacokinetic Modeling and Probability of Pharmacodynamic Target Attainment for Ceftazidime-Avibactam in Pediatric Patients Aged 3 Months and Older

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**Increasing prevalence of infections caused by antimicrobial-resistant gram-negative bacteria represents a global health crisis, and while several novel therapies that target various aspects of antimicrobial resistance have been introduced in recent years, few are currently approved for children. Ceftazidime-avibactam is a novel β-lactam β-lactamase inhibitor combination approved for adults and children 3 months and older with complicated intra-abdominal infection, and complicated urinary tract infection or hospital-acquired ventilator-associated pneumonia (adults only in the United States) caused by susceptible gram-negative bacteria. Extensive population pharmacokinetic (PK) data sets for ceftazidime and avibactam obtained during the adult clinical development program were used to iteratively select, modify, and validate the approved adult dosage regimen (2,000–500 mg by 2-hour intravenous (IV) infusion every 8 hours (q8h), with adjustments for renal function). Following the completion of one phase I (NCT01893346) and two phase II ceftazidime-avibactam studies (NCT02475733 and NCT02497781) in children, adult PK data sets were updated with pediatric PK data. This paper describes the development of updated combined adult and pediatric population PK models and their application in characterizing the population PK of ceftazidime and avibactam in children, and in dose selection for further pediatric evaluation. The updated models supported the approval of ceftazidime-avibactam pediatric dosage regimens (all by 2-hour IV infusion) of 50–12.5 mg/kg (maximum 2,000–500 mg) q8h for those ≥6 months to 18 years old, and 40–10 mg/kg q8h for those ≥3 to 6 months old with creatinine clearance > 50 mL/min/1.73 m$^2$.**

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ There is currently limited information on optimal ceftazidime-avibactam dosage regimens for pediatric patients.

### WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Pharmacokinetic (PK) data for ceftazidime and avibactam from three pediatric studies were added to an adult population PK database. PK models were adapted for children and used to simulate pediatric ceftazidime-avibactam doses with the aim of achieving similar area under the plasma concentration-time curve (AUC), maximum plasma concentration ($C_{max}$), and joint pharmacokinetic/pharmacodynamic (PD) target attainment values to those adults with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), or hospital-acquired pneumonia ventilator-associated pneumonia (HAP/VAP) receiving approved doses.

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Ceftazidime-avibactam pediatric dosages (≥6 months to <18 years: 50–12.5 mg/kg; ≥3 to <6 months old: 40–10 mg/kg (every 8 hours by 2-hour intravenous infusions)) for patients with cIAI or cUTI and normal renal function or mild renal impairment achieved exposures and probability of target attainment generally comparable to those in adults. Simulations for a HAP/VAP pediatric population were supportive of using the same dosing regimens.

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This work supports ceftazidime-avibactam dosing for treating infections with susceptible gram-negative organisms in pediatric patients (3 months to 18 years old).

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Increasing prevalence of infections caused by multidrug resistant (MDR) gram-negative bacteria, combined with limited availability of treatment options and compounded by the lack of novel antibiotic discovery, constitute an urgent threat to global public health.[1–3] Of particular concern is the emergence of MDR strains of *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.[1] The increasing incidence of MDR gram-negative infections among children, particularly those caused by carbapenem-resistant organisms, highlights the need for novel antimicrobial therapies for the pediatric population in the context that few antimicrobial agents addressing MDR gram-negative pathogens are currently approved for children.[4–7] Ceftazidime is an established cephalosporin/β-lactam which has been widely used in adults and children for more than two decades. Ceftazidime-avibactam addresses resistance in MDR gram-negative bacteria mediated by Ambler class A (e.g., extended-spectrum ß-lactamases and *Klebsiella pneumoniae* serine-carbapenemases), class C (e.g., AmpC cephalosporinases), and some class D (e.g., oxacillinase-48) enzymes, but not those expressing metallo-β-lactamases (e.g., New Delhi metallo-β-lactamase) or *Acinetobacter* oxacillinase-type carbapenemases.[8–11]

In Europe, ceftazidime-avibactam is approved for treatment of adults and children ≥ 3 months old with complicated urinary tract infection (cUTI) including pyelonephritis; complicated intra-abdominal infection (cIAI; in combination with metronidazole); hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP); and bacteremia associated with the above indications. It is also approved for infections due to aerobic gram-negative organisms with limited treatment options.[12] In the United States, ceftazidime-avibactam is approved for the treatment of adults and children ≥ 3 months old with cIAI and cUTI, and for adults with HAP/VAP.[13] Ceftazidime-avibactam is administered in a fixed 4:1 ratio by 2-hour intravenous (IV) infusions. The standard adult dose is 2,000–500 mg every 8 hours (q8h); as both ceftazidime and avibactam are predominantly renally cleared, doses are adjusted for patients with estimated creatinine clearance (CrCL) < 50 mL/min. Ceftazidime-avibactam was approved for adults based on an extensive clinical trial program (including 5 phase III, 2 phase II, and 11 phase I clinical trials), accompanied by iterative population pharmacokinetic (PK) modeling and exposure and probability of pharmacodynamic (PD) target attainment (PTA) simulations to select, optimize, and validate the approved dosing regimens, including adjustments for renal impairment.[14,15]

Following completion of one phase I and two phase II pediatric clinical trials, including initial pediatric population PK modeling to select doses for phase II,[16–19] European and US approvals of ceftazidime-avibactam were extended to include dosing recommendations for children ≥ 3 months old.[12,13] Updated adult and pediatric population PK models, described here, were developed to evaluate ceftazidime and avibactam exposures including subject covariate effects, in children ≥ 3 months to < 18 years old. Monte Carlo simulations based on the updated models were used to evaluate dosage recommendations for children with cUTI, cIAI, or HAP, including VAP.

## METHODS

### Informed consent and ethics

All clinical studies included in these population PK analyses were conducted in accordance with the ethical standards of the responsible committee on human experimentation or with the Helsinki Declaration of 1975 (as revised in 1983), and received ethics approval from relevant institutional committees. Informed consent was obtained for all participants.

### Analysis data

Existing adult two-compartment population PK models for ceftazidime and avibactam[15] were updated with PK data from a phase I single-dose pediatric study (NCT01893346)[16] and two phase II multiple-dose studies in children with cIAI (NCT02475733) or cUTI (NCT02497781).[17,18] An overview of the pediatric studies including dosing cohorts and PK sampling schedules is shown in **Table S1**. For subjects with estimated CrCL ≥ 50 mL/min, ceftazidime-avibactam doses were 2,000–500 mg (≥ 12 to < 18 years), 50–12.5 mg/kg (≥ 3 months to 18 years), and 40–10 mg/kg (≥ 3 to 6 months); doses were capped to the standard adult dose (2,000–500 mg) for patients ≥ 40 kg. Of note, doses for phase II patients ≥ 3 months to <1 year old (40–10 mg/kg) differed from those in the phase I study (50–12.5 mg/kg) after initial modeling.[19] Analyte concentrations were measured using validated liquid chromatography with tandem mass spectrometric detection methods.[20–22] For all pediatric studies, the lower limit of quantification was 50 ng/mL for ceftazidime and 10 ng/mL for avibactam. Concentration samples with missing corresponding dosing data, or with missing time or date information, were excluded from the analysis. Concentration samples below the assay quantitation limit (BLQ) were treated as missing if associated with the first predose sample and excluded from the analysis, and were imputed to half the lower limit of quantification for postdose BLQ observations for adults only. There were no observed BLQ samples in the phase II pediatric studies. BLQ concentrations at ~ 24 hours after the start of infusion in Cohort 1 in the phase I pediatric study were omitted.

### Modeling software

The first-order conditional estimation with interaction (FOCE-INTER) method in nonlinear mixed-effects modeling (NONMEM) 7.3 (Icon Development Solutions, Hanover, MD) was the primary method used for population PK model development (see **Supplementary Methods**). For avibactam, the final model was obtained via a two-stage stochastic approximation of expectation-maximization/importance sampling expectation maximization assisted by mode *a posteriori* algorithm to obtain more reliable parameter standard error estimates. FOCE-INTER was used for the final ceftazidime model. R (R-project, R Foundation for Statistical Computing, Vienna, Austria, www.rproject.org, v3.4.3) was used for PTA simulations to evaluate pediatric ceftazidime-avibactam dose recommendations. Simulations were based on the final ceftazidime and avibactam population PK models. SAS (v9.4 or higher; SAS Institute Inc., Cary, NC) or R (v3.3.1 or higher) were also used for data preparation. Xpose (Uppsala Univerity, Uppsala, Sweden, https://uupharmacometrics.github.io/xpose4/) and PsN (Uppsala University, Uppsala, Sweden, https://uupharmacometrics.github.io/PsN) were also used for model diagnostics and facilitation of NONMEM tasks such as bootstrapping and covariate testing.

### Model development

The adult population PK models for ceftazidime and avibactam[15] were adapted for a pediatric population as described below. The population PK analysis utilized ceftazidime and avibactam total (free plus bound) plasma concentrations, individual baseline covariate information, and chronological records of the dosing and plasma sampling history.

To facilitate pediatric predictive performance, two-compartment ceftazidime and avibactam disposition models were adjusted to account for

known differences between adult and pediatric populations, notably those of body size and renal maturation in children ≤ 2 years old. Allometric scaling for body weight was investigated on clearance (CL), intercompartmental clearance (Q), apparent volume of the peripheral compartment ($V_p$), and apparent volume of the central compartment ($V_c$). Initially, allometric exponents were fixed to standard values of 0.75 for CL and Q, and 1 for $V_c$ and $V_p$, with a reference weight of 70 kg; however, during model development, the allometric exponents for CL and Q were changed to 0.67 after estimation and to better reflect the renal excretion characteristics of both avibactam and ceftazidime.[23] For ceftazidime this was further adapted to a maximum effect ($E_{max}$)-type function in the final model (see **Supplementary Methods**). For children > 2 years old, the impact of renal function was accounted for by using body surface area–normalized CrCL (NCrCL), calculated using the updated bedside Schwartz formula.[24,25] For children ≤2 years old, the renal maturation function used postmenstrual age in place of NCrCL (wherein patients ≤ 2 years old achieved 50% of maturation at 47.7 weeks with a sigmoidicity parameter of 3.4).[26] Where postmenstrual age was unknown, it was assumed to be postnatal age +40 weeks. Estimated CrCL in adults (calculated using the Cockcroft–Gault formula[27]) was adjusted for body surface area to reflect NCrCL with units of mL/min/1.73 $m^2$.

Prior to covariate model building, exploratory graphical analysis was used to identify unusual patterns and/or data points in the pediatric studies. Observations for which the absolute value of the associated conditional weighted residual (CWRES) was > 4 were defined as outliers and excluded. After covariate model building, various variance-covariance matrices of random effects were evaluated, and the final population PK models were run with and without outliers. For avibactam, the base model also excluded observations based on visual exploration.

Allometric scaling, NCrCL, and the renal maturation function were *a priori* incorporated and retained in the covariate base model. Covariates previously identified with adult data alone were re-evaluated and additional covariates were tested through a forward inclusion process at significance level $P = 0.05$, followed by a backward elimination with a criterion of $P = 0.01$.

### Model evaluation

Diagnostic plots were generated to evaluate the adequacy of the goodness of fit for PK models. Nonparametric bootstrap resampling methods were used to validate stability of the final population PK models and estimate confidence intervals for the model parameters. Point population estimates, median values, and 90% confidence intervals for each parameter were obtained from 500 bootstrap data sets for avibactam, and 200 bootstrap data sets for ceftazidime. Performance of the final models was assessed by prediction-corrected visual predictive checks (pcVPC) stratified by pediatric vs. adult subjects, age, weight, NCrCL, and indication.

### PK parameter calculations

Using empirical Bayes estimates (EBEs) in NONMEM, secondary PK parameters including maximum plasma concentration at steady state ($C_{max,ss}$), minimum plasma concentration at steady state ($C_{min,ss}$), area under the plasma concentration-time curve over a dosing interval from 0 to 8 hours at steady state, and area under the plasma concentration-time curve over 24 hours at steady state ($AUC_{ss,0-24}$) were calculated for all pediatric and adult patients.

### Simulations and PK/PD targets

Ceftazidime and avibactam free plasma concentration-time courses (assuming 85% and 92% free fractions for ceftazidime and avibactam, respectively) were simulated for all patients with evaluable PK data to ascertain joint PK/PD target attainment across a range of minimum inhibitory concentrations (MICs) for ceftazidime-avibactam against *Enterobacterales* and *P. aeruginosa*. A joint PK/PD target of 50% of dose interval that free concentrations ($fT$) > MIC of 8.0 mg/L for ceftazidime (with avibactam) and 50% of dose interval that free avibactam concentrations are greater than threshold concentration ($C_T$) of 1.0 mg/L ($fT > C_T$ of 1.0 mg/L) , achieved simultaneously, was selected as the primary PK/PD target for the adult ceftazidime-avibactam program based on *in vitro* and animal model data.[15,28,29] As similar pathogens and disease processes are involved in both adult and pediatric infections, the same joint PK/PD target was used for evaluating pediatric dosing regimens.

### PTA analyses

The final population PK models were used to simulate pediatric patients > 2 to < 18 years old with cIAI, cUTI, or HAP/VAP and normal renal function (NCrCL ≥ 80 mL/min/1.73 $m^2$), or mild renal impairment (50 to < 80 mL/min/1.73 $m^2$) receiving various ceftazidime-avibactam dosage regimens. Each simulation included 1,000 patients per indication, age cohort, and dose group. Simulations for patients ≥ 3 months to ≤ 2 years old used the renal maturation function described above. Adults with normal renal function or mild renal impairment receiving ceftazidime-avibactam 2,000–500 mg q8h (simulated using the updated models) were used as reference populations.

Demographic data (including body weight, age, and NCrCL) from distributions for patients > 2 to < 18 years old were bootstrapped from a Pfizer internal covariate distribution database of children ($n$ = 457) with infections from ceftazidime-avibactam and other drug development programs for bacterial infections. Distributions of age, body weight, and length were derived from Centers for Disease Control and Prevention growth charts for patients ≤ 2 years old.[30]

To account for the correlation between the elimination of ceftazidime and avibactam, between-subject variability (BSV) was simulated nonparametrically through resampling of individual *post hoc* random effect estimates from the final ceftazidime and avibactam PK models for the same individual.[15] Pediatric random effects were applied to pediatric simulated subjects and adult random effects to adults. As shrinkage of random effects toward the median of *post hoc* parameters has the potential to underestimate BSV and introduce bias in PTA, *post hoc* random effect estimates were reinflated using a factor inversely proportional to the shrinkage estimates from NONMEM.[15]

PTA for each simulated age group was calculated for a range of MICs as the percentage of 1,000 simulated patients who achieved the joint PK/PD target for a range of doses. Results of simulations for the doses used in the phase II pediatric cIAI and cUTI studies (and which were subsequently approved) are presented. Simulations for pediatric patients with moderate or severe renal impairment, or end-stage renal disease, will be reported separately (Franzese *et al*., in preparation).

## RESULTS

### Model data sets

Of 160 patients enrolled in the pediatric studies, 6 had no evaluable PK observations (1 because height was not measured for the key covariate of NCrCL), and 1 had evaluable PK observations for ceftazidime only. Regarding outliers, 30 adult and 3 pediatric ceftazidime concentrations had absolute CWRES > 4; 17 pediatric avibactam concentrations had absolute CWRES > 4 (< 0.1% of observations). Although inclusion of outliers had little impact (< 15% change) on most model parameter estimates, they increased BSV (> 40%) on Q and $V_c$ and additive residual error for phase II and III for ceftazidime, and for avibactam they changed the population effects on $V_c$ by > 15%. Outliers were therefore excluded in both final models.

After data exclusions, 509 observations for ceftazidime and 488 observations for avibactam, from 153 pediatric patients, were added to the existing adult population PK data sets. In total, there were 9,628 observations and 2,130 subjects in the updated

ceftazidime analysis, and 14,223 observations and 2,403 subjects in the updated avibactam analysis. Demographic characteristics for the adult population have been reported;[15] those for the pediatric population are shown in **Table 1**. In the phase II pediatric cIAI study, no patients were enrolled with NCrCL < 50 mL/min/1.73 $m^2$, and in the phase II pediatric cUTI study, one patient in the ceftazidime-avibactam arm was enrolled with NCrCl < 50 mL/min/1.73 $m^2$. Moreover, no patients < 2 years old were enrolled into the ceftazidime-avibactam arm of the phase II pediatric cIAI study (see **Table S1**). Observed concentration vs. time plots for all pediatric patients (dose normalized to ceftazidime-avibactam 50–12.5 mg/kg to maximum 2,000–500 mg) are shown in **Figure S1**.

### Final population PK models

The pooled pediatric and adult PK data for ceftazidime and avibactam were each well described by a two-compartment disposition model with first-order elimination from the central compartment following IV infusion. Goodness-of-fit plots for ceftazidime and avibactam indicated that the final models exhibited minimal bias (**Figure S2**). In addition, no trends were observed in the random effects vs. covariates plots, indicating a good characterization of the covariate relationships in the final models. The population PK models performed well as indicated by pcVPC, both overall and stratified by pediatric vs. adult subjects, or (for pediatric patients), age, body weight, NCrCL, and disease indication (**Figures S3–S7**), indicating that the models were suitable for simulating exposures and joint PTA in the patient populations of interest.

**Ceftazidime.** Final ceftazidime population PK model parameters are shown in **Table S2**. The effect of weight on Q, $V_c$, and $V_p$ was implemented using power covariate models with fixed exponents of 0.67, 1.0, and 1.0, respectively. Initially, the effect of weight on CL was also modeled using a power model with a fixed allometric scaling exponent of 0.67. However, exploratory graphical analysis of individual EBEs of the base model vs. individual covariates identified a strong bias in CL random effects with low body weight. To optimize the final model for the effect of weight on CL, an $E_{max}$-type model was used as it gave a better fit for younger subjects. This is further described in the **Supplementary Materials**. In general, the fixed-effect parameters were estimated with good precision, with relative standard errors (RSEs) < 30% (**Table S2**).

**Avibactam.** Final avibactam population PK model parameters are shown in **Table S3**. The effect of weight on CL, Q, $V_c$, and $V_p$ was implemented using allometric scaling with fixed exponents (0.67 for CL and Q, and 1 for central and peripheral volumes). As for ceftazidime, maturational changes in the renal function of very young children (≤ 2 years old) were described using the Rhodin equation (fixed parameters).[26] All fixed-effect parameters were estimated with good precision (all RSEs < 30%) except for the effect of cIAI on CL in adults from phase II (RSE = 33%), and that on $V_c$ of mechanical ventilation on the day of PK sampling for adults in the phase III HAP/VAP trial (RSE = 56%). The unexplained BSV variances were also well estimated, with all RSEs < 40% except for the effect on Q (47.8%). Residual error terms were estimated with moderate to high precision.

### Predicted exposures from the final population PK models

Predicted $AUC_{ss,0-24}$, $C_{max,ss}$, and $C_{min,ss}$ for all phase III adults and phase I–II children in the analysis data set, and individual attainment rates of the joint PK/PD target, are shown in **Table 2**. Predicted vs. observed exposures by body weight are shown in **Figure 1**. Mean ceftazidime and avibactam $AUC_{ss,0-24}$, $C_{max,ss}$, and $C_{min,ss}$ for adult phase III cUTI, cIAI, and HAP/VAP patients estimated using the updated models were within ±4% of those in the previous adult population PK models, and rates of joint target attainment for these patients were within ±0.2% of the previous values.[15] For most phase II pediatric study cohorts, model-predicted mean $AUC_{ss,0-24}$ values for both ceftazidime

**Table 1 Baseline characteristics of patients included in the ceftazidime-avibactam pediatric modeling and simulations**

| Parameter | Phase I suspected/ confirmed infection | Phase II cIAI | Phase II cUTI | Overall |
|---|---|---|---|---|
| *N* | 32 | 58 | 63 | 153 |
| Females, *n* (%) | 17 (53.1) | 16 (27.6) | 52 (82.5) | 85 (55.6) |
| Age, years, median (range) | 5.7 (0.33–17.3) | 10.5 (3.00–17.0) | 3.8 (0.25–17.7) | 7.57 (0.250–17.7) |
| Weight, kg, median (range) | 20.6 (5.40–60.5) | 37.9 (15.4–80.0) | 15.3 (4.1–71.0) | 25.0 (4.1–80.0) |
| BSA, $m^2$, median (range) | 0.855 (0.32–1.70) | 1.27 (0.691–2.03) | 0.655 (0.26–1.85) | 0.961 (0.26–2.03) |
| Baseline NCrCL, mL/min/1.73 $m^2$, median (range) | 130.0 (85.5–489.0) | 107.0 (59.0–271.0) | 89.0 (43.0–158.0) | 104 (43.0–489.0) |
| Ethnicity, *n* (%) | | | | |
| White | 24 (75.0) | 51 (87.9) | 46 (73.0) | 121 (79.1) |
| Black | 6 (18.8) | 0 | 0 | 6 (3.9) |
| Asian (non-Chinese, non-Japanese) | 1 (3.1) | 1 (1.7) | 0 | 2 (1.3) |
| Chinese (including Taiwanese) | 0 | 6 (10.3) | 12 (19.0) | 18 (11.8) |
| American Indian or Alaskan Native | 1 (3.1) | 0 | 0 | 1 (0.7) |
| Other | 0 | 0 | 5 (7.9) | 5 (3.3) |

BSA, body surface area; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; NCrCL, normalized creatinine clearance.

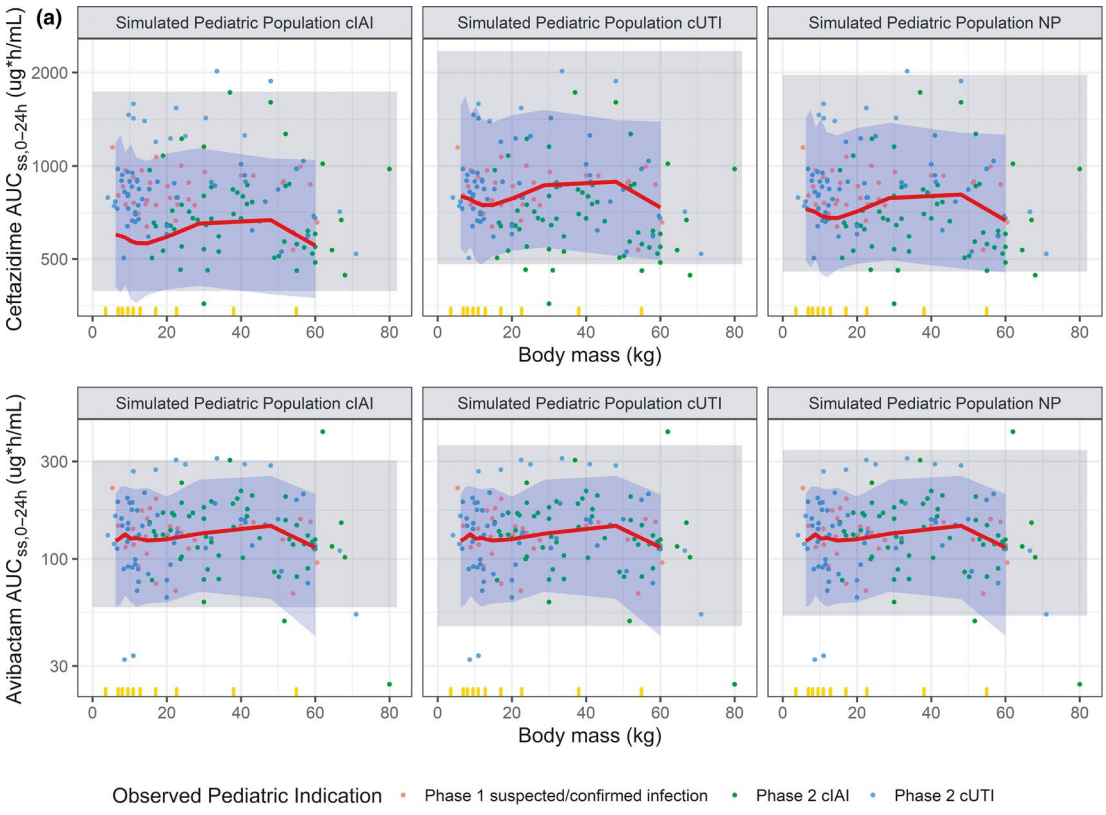
**Table 2 Model-predicted ceftazidime and avibactam steady-state PK exposures and joint target attainment in adults and pediatric populations**

| Age group | Number of ceftazidime/avibactam subjects | Avibactam | | | Ceftazidime | | | Joint target attainment (%) |
|---|---|---|---|---|---|---|---|---|
| | | $C_{min,ss}$ (μg/mL) | $C_{max,ss}$ (μg/mL) | $AUC_{ss,0-24}$ (μg•h/mL) | $C_{min,ss}$ (μg/mL) | $C_{max,ss}$ (μg/mL) | $AUC_{ss,0-24}$ (μg•h/mL) | |
| Adults (phase III) | | | | | | | | |
| cUTI | 638/647 | 973 (44.7) | 14.4 (108) | 80.7 (30.9) | 139 (72.9) | 1.53 (147) | 12.3 (70.2) | 98.7 |
| cIAI | 697/703 | 722 (44.2) | 8.2 (106) | 66.2 (31.1) | 133 (67.4) | 1.12 (134) | 12.9 (67.6) | 98.4 |
| HAP/VAP | 413/413 | 936 (50.4) | 14.7 (108) | 74.8 (37.9) | 174 (81) | 2.27 (134) | 14.7 (77) | 99.0 |
| Pediatric phase I confirmed/suspected infection (single dose) | | | | | | | | |
| ≥3 months to <2 years | 8/8 | 888 (14.5) | 3.44 (50.4) | 106 (9.81) | 143 (22.2) | 0.46 (77.6) | 17.4 (18.2) | 100 |
| ≥2 to <6 years | 8/8 | 794 (16.0) | 2.5 (77.7) | 97.2 (10.6) | 127 (33.8) | 0.3 (114) | 15.9 (31.7) | 100 |
| ≥6 to <12 years | 8/8 | 814 (13.8) | 3.3 (78.7) | 97.7 (8.5) | 121 (23.9) | 0.36 (93.7) | 14.9 (23.1) | 100 |
| ≥12 to <18 years | 8/8 | 821 (21.5) | 4.36 (64.7) | 95.2 (15.3) | 124 (29.9) | 0.47 (77.1) | 15.2 (27.6) | 100 |
| Pediatric phase II cIAI (multiple dose) | | | | | | | | |
| ≥2 to <6 years | 6/6 | 607 (27.1) | 1.71 (82) | 75.6 (19.2) | 119 (24.7) | 0.35 (58.6) | 14.4 (24.6) | 100 |
| ≥6 to <12 years | 33/33 | 729 (31.6) | 3.85 (123) | 81 (17.8) | 147 (34.5) | 0.67 (119) | 16.5 (32.9) | 97.0[a] |
| ≥12 to <18 years | 19/19 | 642 (33.3) | 4.55 (105) | 67.7 (17.4) | 105 (59.1) | 0.57 (62.5) | 11.5 (77.5) | 94.7[a] |
| Pediatric phase II cUTI (multiple dose) | | | | | | | | |
| ≥3 to <6 months | 5/5 | 736 (24.4) | 4.68 (78.6) | 78.1 (15.9) | 132 (30.5) | 0.91 (17) | 13.8 (36.8) | 100 |
| ≥6 months to <1 year | 9/9 | 859 (23.1) | 5.14 (80.9) | 92.3 (9.72) | 113 (58.3) | 0.55 (85.2) | 12.5 (63.1) | 100 |
| ≥1 to <2 years | 11/11 | 883 (30.8) | 5.57 (121) | 92.8 (12.9) | 117 (62.2) | 0.6 (254) | 12.5 (46.8) | 90.9[a] |
| ≥2 to <6 years | 10/10 | 789 (19.7) | 3.18 (50.3) | 94.1 (15) | 123 (43.3) | 0.47 (47.4) | 14.6 (50.5) | 100 |
| ≥6 to <12 years | 16/16 | 993 (35.6) | 7.02 (109) | 104 (22) | 153 (43.4) | 0.76 (110) | 17.1 (38.3) | 100 |
| ≥12 to <18 years | 12/12 | 843 (39.1) | 6.06 (84.9) | 92.4 (27.4) | 139 (55.3) | 0.66 (65.6) | 16.4 (60.9) | 100 |

Values are geometric mean (%CV). $C_{max,ss}$ is obtained at the end of infusion. $C_{min,ss}$ is obtained 8 hours after the start of infusion. The joint PK/PD target was 50% *f*T >8.0 mg/L for ceftazidime and 50% *f*T >1.0 mg/L for avibactam. See **Table S1** for doses used in the pediatric studies.

$AUC_{ss,0-24}$, total daily area under the plasma concentration-time curve at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{min,ss}$, minimum plasma concentration at steady state; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; *f*T, time that free concentrations are above MIC or threshold; HAP, hospital-acquired pneumonia; PD, pharmacodynamic; PK, pharmacokinetic; VAP, ventilator-associated pneumonia.

[a]One subject in each of these cohorts did not achieve the joint PK/PD target.


(a)
Simulated Pediatric Population cIAI
Simulated Pediatric Population cUTI
Simulated Pediatric Population NP
Ceftazidime AUCss,0–24h (ug*h/mL)
2000
1000
500
0
20
40
60
80
Body mass (kg)
Avibactam AUCss,0–24h (ug*h/mL)
300
100
30
Observed Pediatric Indication
Phase 1 suspected/confirmed infection
Phase 2 cIAI
Phase 2 cUTI

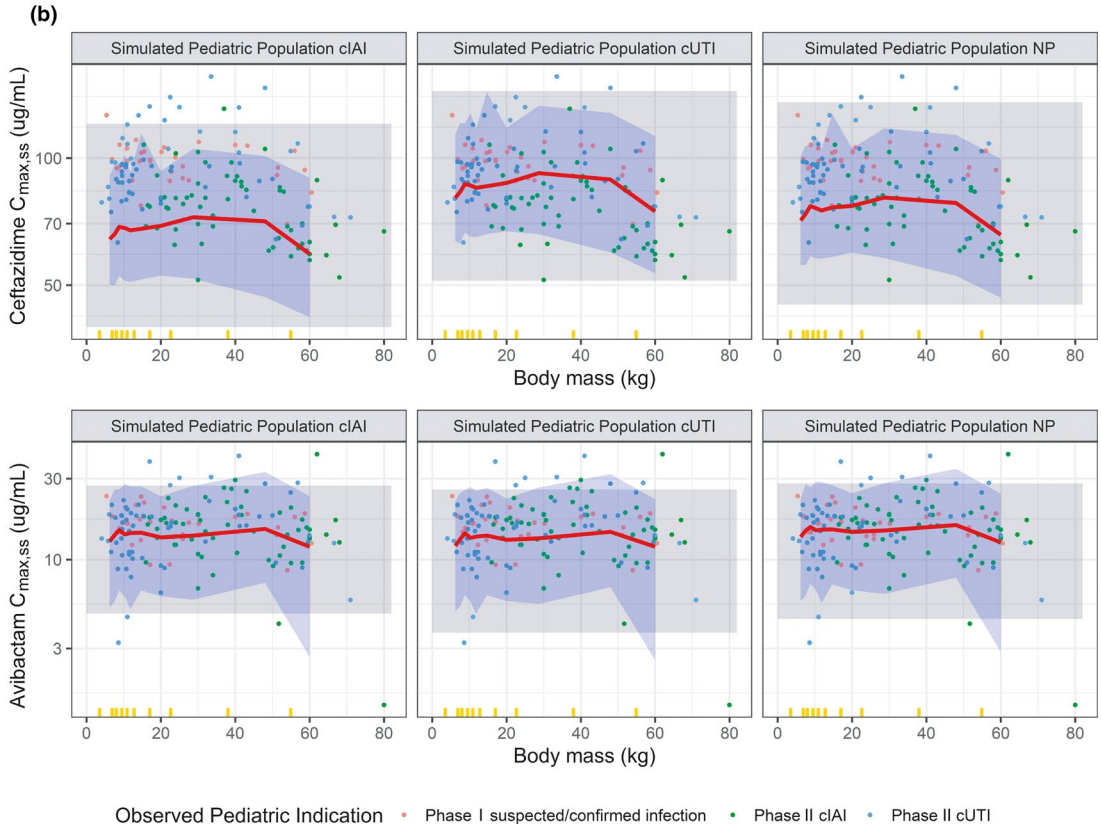

(b)
Simulated Pediatric Population cIAI
Simulated Pediatric Population cUTI
Simulated Pediatric Population NP
Ceftazidime Cmax,ss (ug/mL)
100
70
50
0
20
40
60
80
Body mass (kg)
Avibactam Cmax,ss (ug/mL)
30
10
3
Observed Pediatric Indication
Phase I suspected/confirmed infection
Phase II cIAI
Phase II cUTI

**Figure 1** Observed (points) and simulated ceftazidime and avibactam steady-state exposures by body weight and indication for pediatric subjects (blue shaded area), compared with simulated adult populations (gray shaded area). (**a**) $AUC_{ss,0-24}$; (**b**) $C_{max,ss}$. $AUC_{ss,0-24}$, total daily area under the plasma concentration-time curve at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection, NP, nosocomial pneumonia. Each symbol represents an individual exposure variable. The red line represents the median simulated values, blue shading represents the 90% prediction interval for each pediatric indication, and gray shading represents the 90% prediction interval for adults with normal renal function or mild renal impairment.

and avibactam deviated from adults by ± 15%. Mean $C_{min,ss}$ values for ceftazidime and avibactam were lower in all pediatric cohorts compared with adults, and mean $C_{max,ss}$ values tended to be higher than in adults. Only three children in different age cohorts did not meet the joint target for an MIC of 8 mg/L (**Table 2**).

### Exposure and PTA simulations

Ceftazidime and avibactam exposures ($C_{max,ss}$ and $AUC_{ss,0-24}$) in simulated adults (receiving ceftazidime-avibactam 2,000–500 mg q8h) and children ≥ 3 months to < 18 years old (receiving the approved pediatric doses) with normal renal function or mild renal impairment are shown in **Table 3**, and joint PTAs for these dosage regimens are shown in **Table 4**. Joint PTA was > 90% for all simulated adults with cUTI, cIAI, or HAP/VAP (similar to the previously reported analyses,[15] despite model adaptation). PTA by MIC curves for the approved ceftazidime-avibactam doses are shown in **Figures S8 and S9**.

In simulated pediatric patients, predicted ceftazidime and avibactam exposures were generally similar to the adult reference population for all age groups (**Table 3**). For children with normal renal function, across indications, mean $C_{max,ss}$ and $AUC_{ss,0-24}$ values were within 92% to 148% of the reference adult values. For those with mild renal impairment, respective values were within 133% to 182% of adults with normal renal function. Joint PTA was > 90% for all simulated pediatric cUTI and HAP/VAP patient age groups, and for all pediatric cIAI patients except those in the 1 to < 2 and 2 to < 6 years-old groups with normal renal function, for whom joint PTA was 82% in both groups (**Table 4**; **Figure S8**).

## DISCUSSION

Efficacy and safety of ceftazidime-avibactam have been demonstrated in well-controlled phase III studies in adults with cIAI, cUTI, and HAP/VAP using the approved dose (2,000–500 mg 2-hour IV infusions q8h for patients with normal renal function/mild renal impairment).[31–37] This extensive adult data set provides clinical validation of the dosing strategy and the resulting plasma exposures required to achieve efficacy.[14,15] The approved ceftazidime-avibactam pediatric doses (50–12.5 mg/kg q8h for patients ≥ 6 months to < 18 years old; 40–10 mg/kg q8h for patients ≥ 3 to < 6 months old) achieved clinical and microbiological response rates of > 90% in children with cIAI, and >88% in those with cUTI in the phase II pediatric trials.[17,18] These regimens are based on exposure-matching to adults and are within the range of approved doses for ceftazidime alone. Of note, ceftazidime-avibactam 40–10 mg/kg q8h for patients ≥ 3 to < 6 months old was selected for further evaluation in the phase II pediatric trials, rather than the 50–12.5 mg/kg evaluated in the single-dose phase I pediatric trial.[16] This was based on an earlier population PK modeling analysis following the phase I pediatric trial, which found that for simulated cIAI and cUTI patients ≥ 3 to < 6 months old, 40–10 mg/kg q8h gave exposures comparable to 50–12.5 mg/kg q8h in patients ≥ 6 months old.[19] The current analyses demonstrate that the approved ceftazidime-avibactam dosage regimens achieved exposures and PTA in children with cIAI and cUTI generally comparable to those in adults. Moreover, simulations for a HAP/VAP pediatric population were supportive of using the same ceftazidime-avibactam doses across all pediatric indications (recommended adult doses are also the same across approved indications).[12,13]

Recent developments in translational modeling and computational capacity have highlighted the limitations of using a "fixed" PK/PD target approach for antimicrobial dosing models, and expanding the use of innovative mechanism-based models has the potential to improve the precision of dose selection and optimization across different patient populations, infection types, and pathogen species.[38] Nevertheless, the current analyses, along with the efficacy and safety findings from the completed pediatric trials,[16–18] supported the recent addition of pediatric dosing recommendations for ceftazidime-avibactam in Europe and the United States for patients ≥ 3 months old (cUTI and cIAI only in the United States).[12,13] The approved ceftazidime-avibactam doses for children with normal renal function or mild renal impairment are those evaluated in the phase II trials.[17,18]

It is important to note that ceftazidime-avibactam has not been evaluated in children with HAP/VAP, although ceftazidime alone has been used for more than 20 years. The simulations assumed that age and weight covariates are common to the pediatric population irrespective of the site of infection, and that adult HAP/VAP covariates would also apply to the pediatric population with HAP/VAP. The lack of subject-level PK data for children with HAP/VAP thus represents a limitation of the current analysis. More broadly, the analyses assumed that tissue penetration of free drug to the sites of infection (lung parenchyma or epithelial lining fluid in HAP/VAP, intra-abdominal compartments in cIAI, and urinary tract concentrations in cUTI) in children is the same as adults. Nevertheless, for infectious processes where the causative pathogens and course of disease are similar between adult and pediatric populations, the value of extrapolation of efficacy and safety of adult clinical trial data to pediatric populations based on exposure-matching and population PK modeling is recognized; a similar rationale supports extrapolating safety and efficacy for pediatric cIAI or cUTI patients to those with HAP/VAP given the same dosing regimens and predicted exposures.[39–42] A further limitation is that there were no pediatric cIAI patients <2 years old enrolled; thus the PK estimates for this age group are based on scaling

**Table 3 Simulated ceftazidime and avibactam PK exposures in patients with normal renal function or mild renal impairment**

| Renal function | Age group | Ceftazidime-avibactam dose | cIAI | | cUTI | | HAP/VAP | |
|---|---|---|---|---|---|---|---|---|
| | | | $C_{max,ss}$ (μg/mL) | $AUC_{ss,0-24}$ (μg•h/mL) | $C_{max,ss}$ (μg/mL) | $AUC_{ss,0-24}$ (μg•h/mL) | $C_{max,ss}$ (μg/mL) | $AUC_{ss,0-24}$ (μg•h/mL) |
| Normal | | | Ceftazidime | | | | | |
| | 12 to <18 years | 50–12.5 mg/kg q8h | 64.6 (24.1) | 618 (30.4) | 81.5 (23.9) | 821 (30.4) | 71.8 (24.1) | 747 (30.4) |
| | 6 to <12 years | 50–12.5 mg/kg q8h | 72.4 (19.6) | 650 (29.8) | 91.5 (19.4) | 864 (29.8) | 80.8 (19.6) | 785 (29.8) |
| | 2 to <6 years | 50–12.5 mg/kg q8h | 68.2 (21.1) | 572 (29.9) | 86.3 (20.8) | 760 (29.9) | 76.4 (21.0) | 691 (29.9) |
| | 1 to <2 years | 50–12.5 mg/kg q8h | 68.1 (19.4) | 577 (29.8) | 86.0 (19.1) | 767 (29.8) | 76.2 (19.2) | 698 (29.8) |
| | 6 to <12 months | 50–12.5 mg/kg q8h | 72.1 (19.5) | 637 (29.9) | 90.8 (19.2) | 846 (29.9) | 80.4 (19.4) | 769 (29.9) |
| | 3 to <6 months | 40–10 mg/kg q8h | 64.2 (19.4) | 617 (30.2) | 80.7 (19.2) | 820 (30.2) | 71.4 (19.4) | 745 (30.2) |
| | Adults | 2,000–500 mg q8h | 58.9 (30.4) | 602 (40.7) | 74.0 (29.9) | 828 (47.8) | 65.1 (31.0) | 712 (41.8) |
| | | | Avibactam | | | | | |
| | 12 to <18 years | 50–12.5 mg/kg q8h | 12.3 (67.7) | 121 (51.1) | 11.9 (68.0) | 121 (51.1) | 13.0 (67.5) | 121 (51.1) |
| | 6 to <12 years | 50–12.5 mg/kg q8h | 14.2 (44.3) | 136 (36.0) | 13.7 (44.7) | 136 (36.0) | 15.1 (43.2) | 136 (36.0) |
| | 2 to <6 years | 50–12.5 mg/kg q8h | 13.0 (49.8) | 118 (41.3) | 12.5 (50.6) | 118 (41.3) | 13.8 (48.9) | 118 (41.3) |
| | 1 to <2 years | 50–12.5 mg/kg q8h | 13.6 (53.5) | 125 (42.8) | 12.9 (53.9) | 125 (42.8) | 14.4 (52.8) | 125 (42.8) |
| | 6 to <12 months | 50–12.5 mg/kg q8h | 14.0 (53.7) | 132 (43.2) | 13.3 (54.1) | 132 (43.2) | 14.9 (53.1) | 132 (43.2) |
| | 3 to <6 months | 40–10 mg/kg q8h | 12.1 (54.1) | 121 (43.5) | 11.5 (54.4) | 121 (43.5) | 12.9 (53.6) | 121 (43.5) |
| | Adults | 2,000–500 mg q8h | 10.5 (81.7) | 107 (68.8) | 9.73 (65.7) | 113 (69.9) | 10.2 (77.6) | 105 (71.8) |
| Mild impairment | | | Ceftazidime | | | | | |
| | 12 to <18 years | 50–12.5 mg/kg q8h | 81.6 (25.6) | 940 (34.0) | 103.0 (25.5) | 1,250 (34.0) | 90.9 (25.7) | 1,140 (34.0) |
| | 6 to <12 years | 50–12.5 mg/kg q8h | 93.4 (20.5) | 1,020 (32.1) | 118.0 (20.4) | 1,350 (32.1) | 104.0 (20.6) | 1,230 (32.1) |
| | 2 to <6 years | 50–12.5 mg/kg q8h | 88.2 (21.7) | 892 (31.8) | 111.0 (21.5) | 1,190 (31.8) | 98.0 (21.8) | 1,080 (31.8) |
| | Adults | 2,000–500 mg q8h | 74.9 (31.9) | 917 (42.1) | 94.3 (32.6) | 1,240 (49.5) | 83.8 (33.0) | 1,100 (43.9) |
| | | | Avibactam | | | | | |
| | 12 to <18 years | 50–12.5 mg/kg q8h | 14.7 (68.4) | 164 (54.2) | 14.2 (68.3) | 164 (54.2) | 15.5 (68.7) | 164 (54.2) |
| | 6 to <12 years | 50–12.5 mg/kg q8h | 17.4 (45.2) | 192 (37.4) | 16.7 (45.3) | 192 (37.4) | 18.5 (44.5) | 192 (37.4) |
| | 2 to <6 years | 50–12.5 mg/kg q8h | 15.9 (51.0) | 167 (42.9) | 15.3 (51.5) | 167 (42.9) | 17.0 (50.4) | 167 (42.9) |
| | Adults | 2,000–500 mg q8h | 12.7 (83.8) | 148 (69.7) | 11.8 (66.7) | 152 (71.0) | 12.5 (79.5) | 147 (72.6) |

Values are geometric mean (%CV). All ceftazidime-avibactam doses were simulated as 2-hour intravenous infusions with a maximum dose of 2,000 mg ceftazidime and 500 mg avibactam. Normal renal function defined as NCrCL ≥ 80 mL/min/1.73 $m^2$. Mild renal impairment defined as NCrCL 51 to <80 mL/min/1.73 $m^2$.

$AUC_{ss,0-24}$, total daily area under the plasma concentration-time curve at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia: NCrCL, normalized creatinine clearance; PK, pharmacokinetic; q8h, every 8 hours; VAP, ventilator-associated pneumonia.

**Table 4 Joint PTA for simulated patients with cIAI, cUTI, or HAP/VAP and normal renal function or mild renal impairment**

| Renal function | Age group | Ceftazidime-avibactam dose | Joint PTA at an MIC of 8 mg/L (%) | | |
|---|---|---|---|---|---|
| | | | cIAI | cUTI | NP |
| Normal | 12 to <18 years | 50–12.5 mg/kg q8h | 96 | 99 | 99 |
| | 6 to <12 years | 50–12.5 mg/kg q8h | 90 | 97 | 97 |
| | 2 to <6 years | 50–12.5 mg/kg q8h | 82 | 94 | 92 |
| | 1 to <2 years | 50–12.5 mg/kg q8h | 82 | 94 | 92 |
| | 6 to <12 months | 50–12.5 mg/kg q8h | 90 | 98 | 97 |
| | 3 to <6 months | 40–10 mg/kg q8h | 93 | 98 | 98 |
| | Adults | 2,000–500 mg q8h | 95 | 97 | 95 |
| Mild impairment | 12 to <18 years | 50–12.5 mg/kg q8h | 99 | 99 | 99 |
| | 6 to <12 years | 50–12.5 mg/kg q8h | 100 | 100 | 100 |
| | 2 to <6 years | 50–12.5 mg/kg q8h | 100 | 100 | 100 |
| | Adults | 2,000–500 mg q8h | 99 | 99 | 99 |

All ceftazidime-avibactam doses were simulated as 2-hour intravenous infusions with a maximum dose of 2,000 mg ceftazidime and 500 mg avibactam. Normal renal function defined as NCrCL ≥ 80 mL/min/1.73 $m^2$. Mild renal impairment defined as NCrCL 51 to < 80 mL/min/1.73 $m^2$.
cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; *f*T, time that free concentration are above MIC or theshold concentration; HAP, hospital-acquired pneumonia; MIC, minimum inhibitory concentration; NCrCL, normalized creatinine clearance; PTA, probability of target attainment (joint target of 50% *f*T > 8.0 mg/L for free ceftazidime (with avibactam) and 50% *f*T > 1.0 mg/L for free avibactam); q8h, every 8 hours; VAP, ventilator-associated pneumonia.

assumptions for weight and renal maturation, cIAI covariate assumptions from adults and older children, and data from pediatric patients < 2 years old with cUTI and other infections. Patients enrolled in the phase II pediatric cIAI study[17] predominantly had appendiceal perforations / peri-appendiceal abscesses; such infections tend to occur most commonly in the second decade of life, and are relatively uncommon in infants and young children compared with older age groups.[43–45]

The population PK models performed well as shown by pcVPCs, both overall and stratified by pediatric vs. adult subjects, age, weight, NCrCL, and disease indication, indicating that the models were suitable for simulating exposures and joint PTA in the pediatric patient populations. Body weight and renal function (renal maturation (subjects ≤ 2 years old) or NCrCL (subjects > 2 years old)) were the key covariates predicting CL of both ceftazidime and avibactam in children. Based on individual EBEs, pediatric patients in this analysis had similar ceftazidime and avibactam $AUC_{ss,0-24}$ values as the adult reference populations. However, mean $C_{min,ss}$ values in children were as low as 31% (avibactam) and 22% (ceftazidime) of the corresponding adult population (cUTI). In contrast, predicted mean $C_{max,ss}$ values tended to be higher in children, up to 139% (avibactam) and 129% (ceftazidime) greater than those of corresponding adults. Based on the model-predicted exposures for subjects in the pediatric trials, joint PK/PD target attainment in pediatric patients (based on the actual doses used in the trials) was 98% across the combined trials. Only three pediatric patients included in the analysis failed to achieve joint target attainment at an MIC of 8 mg/L. However, since *Enterobacterales* and *P. aeruginosa* with ceftazidime-avibactam MIC values ≤ 8 mg/L are considered susceptible,[12,13,28] exposures in these three patients are likely to have attained relevant targets for the actual MICs of the infecting organisms. In a recent US surveillance study of bacteria causing bloodstream infections in pediatric patients, the highest ceftazidime-avibactam MIC value among *Enterobacterales* was 4 mg/L (and 2 mg/L among extended-spectrum ß-lactamase–producers) and 99.2% of isolates were inhibited at ≤ 1 mg/L. Ceftazidime-avibactam exhibited complete activity (100.0% susceptibility) against *P. aeruginosa* with > 90% of isolates inhibited at ≤ 4 mg/L.[46]

For simulated pediatric patients, the ceftazidime-avibactam doses used in the phase II trials were predicted to achieve > 90% PTA in all cUTI and HAP/VAP age groups, and in cIAI patients 6 to < 18 years old and 3 months to < 1 year old; however, the PTA for cIAI patients 1 to < 6 years old was 82%. This may be attributed to: (i) cIAI patients (adult and pediatric) have 33% increased ceftazidime CL; (ii) weight-based scaling of CL ($E_{max}$ model) results in higher ceftazidime CL (mg/kg) in younger vs. older children; (iii) there were few data for patients ≤ 6 years old in the phase II pediatric cIAI study (6 patients > 2 to ≤ 6 years old, 0 patients > 1 to ≤ 2 years old). Of note, alternative dosing regimens beyond those reported here were also simulated to assess whether PTA could be further improved for cIAI patients 1 to < 6 years old; for example, increasing ceftazidime-avibactam dosage by 20% (60–15 mg q8h) improved PTA but not above 90% because of the rate-limiting impact of increased ceftazidime CL for patients with cIAI. Conservative assumptions were used to estimate PTA: the target MIC of 8 mg/L encompasses the majority of target pathogens (up to 99.9% of Enterobacterales and 99.1–100% of *P. aeruginosa*isolates had ceftazidime-avibactam MICs ≤4 mg/L in pediatric surveillance studies[46–48]); re-inflation (increase) of PK variability to overcome shrinkage. Moreover the joint PK/PD target was achieved for the six phase II pediatric cIAI patients < 6 years old; therefore the ceftazidime-avibactam dose of 50–12.5 mg/kg (2-hour IV infusions) q8h is expected to achieve acceptable exposures and PTA for this age group of cIAI patients.

In conclusion, the approved ceftazidime-avibactam pediatric dosage regimens, which were associated with clinical and microbiological efficacy in the phase II cIAI and cUTI trials,[17,18] result in geometric mean exposures and PTA values for simulated pediatric cIAI, cUTI, and HAP/VAP patients ≥ 3 months to < 18 years old consistent with those in simulated adults.[15] Efficacy and safety for children with cUTI, cIAI, or HAP/VAP receiving these doses can therefore be expected to be similar to that in the corresponding adult populations.[37,39–42,49] These analyses supported approval of ceftazidime-avibactam dosage regimens for children with cIAI or cUTI (and HAP/VAP in Europe) and estimated NCrCL > 50 mL/min/1.73 $m^2$ of 50–12.5 mg/kg (maximum 2,000–500 mg) q8h (≥ 6 months to 18 years old), and 40–10 mg/kg q8h (≥ 3 to 6 months), all given by 2-hour IV infusions.[12,13] An ongoing phase II study (NCT04126031) will provide additional data on ceftazidime-avibactam PK in neonates and young infants with bloodstream infections.

## SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).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## CONFLICT OF INTEREST

R.C.F., K.J.W., and M.L. are employees of Certara Strategic Consulting, which received funding from Pfizer for the population PK analyses. P.L.S.C., M.V., and S.R. are employees of and shareholders in Pfizer. L.M. is a former employee of and shareholder in Pfizer. T.R. is an employee of and shareholder in AbbVie. T.J.C. is a former employee of and shareholder in AbbVie. J.S.B.'s employer, the University of California, received institutional funds from AstraZeneca and Pfizer to conduct and consult on the ceftazidime-avibactam pediatric clinical trials.

## AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. M.L., T.R., T.J.C., L.M., P.L.S.C., M.V., S.R., and J.S.B. designed the research. J.S.B., M.L., R.C.F., and K.W. performed the research. M.L, R.C.F., K.W., T.R., T.J.C., L.M., P.L.S.C., M.V., and S.R. analyzed the data.

## DATA AVAILABILITY STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (i) for indications that have been approved in the United States and/or European Union or (ii) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.




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