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# O1163 Ceftazidime-avibactam population pharmacokinetic (PK) and PK-pharmacodynamic (PK/PD) modelling and simulation to support paediatric dosing

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**Background:** PK modelling based on adult clinical trial datasets supported the approved ceftazidime-avibactam dosing regimen of 2000-500 mg by 2-h IV infusion q8h. Adult PK datasets were updated with paediatric PK data from a single-dose study (NCT01893346), and two multiple-dose studies (NCT02475733 and NCT02497781) in complicated intra-abdominal (cIAI) and urinary tract infections (cUTI) and used to characterise the population PK of ceftazidime and avibactam in children.

**Materials/methods:** To facilitate paediatric predictive performance, the adult 2-compartment disposition model was adjusted to include allometric scaling for all subjects and a renal maturation function (Hill function) for subjects ≤2 years. Empirical Bayesian PK parameter estimates were used to compute steady-state maximum/minimum plasma concentrations ($C_{max,ss}$/$C_{min,ss}$), and area under the plasma concentration–time curve over 24 hrs ($AUC_{ss,0–24}$) for adult patients and 153 children (≥3 months to <18 years) for exposure matching. Predicted PK was used with *in vitro* PK/PD targets (free plasma ceftazidime >8 mg/L and free avibactam >1 mg/L for ≥50% of dosing interval) to evaluate probability of joint target attainment (JPTA) across the dose interval. The models were also used for Monte Carlo simulations.

**Results:** Body weight, renal maturation (in subjects ≤2 years) or body surface area-normalised CrCL (in subjects >2 years) were key independent covariates predicting clearance of ceftazidime and avibactam. Visual predictive checks of the final population PK models indicated models were suitable for simulations. In the paediatric studies (doses of 2000-500 mg for >40 kg or 50-12.5 mg/kg >6 months q8h by 2-h infusion), geometric mean ceftazidime and avibactam $AUC_{ss,0–24}$ were similar to the adult reference population, with most study cohorts deviating by no more than ±15%. In children, predicted $C_{min,ss}$ were generally lower, and $C_{max,ss}$ generally higher, for both ceftazidime and avibactam, relative to adults. Of 153 children included, an overall JPTA of 98% was achieved, with the lowest JPTA (90.9%) in the 1–2 year age group (n=11).

**Conclusions:** These population PK models will support labelled paediatric dosage recommendations for cIAI and cUTI and dose selection for further studies in neonates, and in children with nosocomial pneumonia.

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