T-078

Ceftolozane/Tazobactam Dose Selection for Pediatric Patients (birth to <18 years)

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Background

- Ceftolozane/tazobactam is a combination of the novel cephalosporin, ceftolozane, and the beta-lactamase inhibitor, tazobactam.
- It is approved for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in adults at the 1.5 g dose (1.0 g ceftolozane and 0.5 g tazobactam) administered as a 1-hr intravenous (IV) infusion every 8 hours [1].
- A Phase 1 study (ClinicalTrials.gov ID, NCT02266706) was designed to assess the pharmacokinetics (PK) and safety of a single dose of ceftolozane/tazobactam in pediatric patients (ages birth [7 days post-natal] to < 18 years).
- Sparse PK data collected in this study were used to develop ceftolozane and tazobactam population PK models for adult and pediatric subjects and to provide dosing recommendations for upcoming safety and efficacy pediatric clinical trials in cUTI and cIAI.

Methods

- Plasma concentration time data from 12 adult studies (including Phase 2 studies in adult subjects with cUTI or cIAI) and this Phase 1 pediatric study were pooled for population PK analysis.
  - For ceftolozane, data from 452 subjects, including 31 pediatric subjects, were used.
  - For tazobactam, data from 318 subjects including 30 pediatric subjects, were used.
- Population modeling was performed using NONMEM (Ver 7) and first-order conditional with interaction (FOCI) estimation method was used.
- The influence of covariates was evaluated using forward selection followed by backward elimination

Simulation Methodology

- Simulations were performed to obtain exposure and probability of target attainment (PTA) for pediatric patients aged birth (7 days postnatal) to < 18 years with cUTI or cIAI (with eGFR > 50 mL/min/1.73 m^2):
- Simulations used virtual patients created using NHANES and CDC charts.
- The criteria used in evaluating the appropriateness of doses were:
  - 95th percentile of pediatric ceftolozane and tazobactam exposures (AUC and Cmax) at steady state not exceeding the corresponding 95th percentile of adult exposures; and
  - ceftolozane PTA ≥ 90% based on a minimum inhibitory concentration (MIC) of 4 µg/mL (the CLSI breakpoint) for at least 30% of the dosing interval and a tazobactam Day 1 PTA ≥ 90% based on a threshold concentration (Ct) of 1 µg/mL for at least 20% of the dosing interval.
    - These criteria are supported based on PK/PD targets from mouse models and clinical studies [2-4].

Results

- Two-compartment models best described the ceftolozane and tazobactam data.
  - The ceftolozane population PK parameter estimates and visual predictive check (VPC) are shown in Table 1 and Figure 1, respectively.
  - The tazobactam population PK parameter estimates and VPC are shown in Table 2 and Figure 2, respectively.
  - Significant covariates included allometric scaling on clearance (CL), central volume of distribution (Vc), intercompartmental clearance (Q, for tazobactam only), and peripheral volume of distribution (Vp) and renal function on CL.
  - Presence of infection was a covariate on CL for tazobactam.
  - Other covariates tested (age, sex, and race) were not significant.

Results

Table 1. Parameter Estimates and Standard Errors from the Final Population PK Model for Ceftolozane

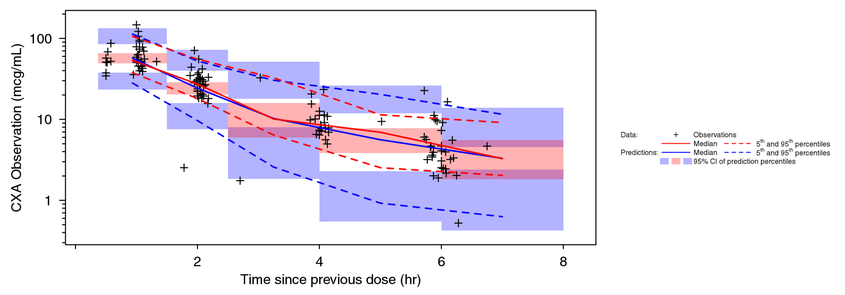
	Final Parameter Estimate				Interindividual Variability / Residual Variability	
Parameter	Typical Value	%SEM	Lower Bound of CI	Upper Bound of CI	Magnitude	%SEM
CL: Systemic clearance (L/h)	5.882	1.567	5.701	6.063	34.61 %CV	15.60
CL: Body weight on CL (Power)	0.7637	8.401	0.6380	0.8895		
CL: MDRD eGFR on CL (Power)	0.7036	8.442	0.5872	0.8200		
V_c: Volume of distribution for central compartment (L)	10.64	2.507	10.11	11.16	44.26 %CV	24.65
V_c: Body weight on V_c (Power)	1.124	6.926	0.9718	1.277		
Q: Intercompartmental clearance (L/h)	2.545[a]	10.62	2.015	3.074	NE	NA
V_p: Volume of distribution for peripheral compartment (L)	4.227[a]	4.466	3.857	4.596	16.33 %CV	46.20
V_p: Body weight on V_p (Power)	0.4840	14.27	0.3487	0.6193		
cov(IIV in V_c, IIV in CL)[b]	0.07624	22.32	0.04289	0.1096	NA	NA
Residual variability proportional	0.02373	14.52	0.01698	0.03049	15.41 %CV	NA
Residual variability additive	0.008780	26.56	0.004210	0.01335	0.09370 SD	NA
Minimum value of the objective function = 18799.471						

Abbreviations: CI, confidence interval; %CV, coefficient of variation expressed as a percentage; eGFR, estimated glomerular filtration rate; IIV, interindividual variability; MDRD, modification of diet in renal disease; NA, not applicable; NE, not estimated; SD, standard deviation; %SEM, standard error of the mean expressed as a percentage.

[a] The following parameter estimates were found to be highly correlated (r^2 = 0.9313).

[b] The calculated correlation coefficient (r) of the off-diagonal omegas was 0.4977 with r^2 = 0.2477 for cov(IIV in V_c, IIV in CL).

Figure 1. VPC for Pediatric Data From the Ceftolozane Final Population PK model



CXA: ceftolozane; Medians and percentiles are plotted at the midpoint of each time since previous dose interval

Table 2. Parameter Estimates and Standard Errors from the Final Population PK Model for Tazobactam

	Final Parameter Estimate				Interindividual Variability / Residual Variability	
Parameter	Typical Value	%SEM	Lower Bound of CI	Upper Bound of CI	Magnitude	%SEM
CL: Systemic clearance (L/h)	20.8[a]	5.81	18.5	23.2	52.9 %CV	24.7
CL: Body weight on CL (Power)	0.652	9.83	0.527	0.778		
CL: MDRD eGFR on CL (Power)	0.733	8.92	0.604	0.861		
CL: Any infection on CL (Proportional)	0.677	14.8	0.481	0.872		
V_c: Volume of distribution for central compartment (L)	12.9[a]	6.18	11.4	14.5	43.9 %CV[b]	54.7
V_c: Body weight on V_c (Power)	0.737	8.43	0.615	0.858		
Q: Intercompartmental clearance (L/h)	4.06	6.03	3.58	4.54	NE	NA
Q: Body weight on Q (Power)	0.75 FIXED	NA	NA	NA		
V_p: Volume of distribution for peripheral compartment (L)	5.06	5.99	4.46	5.65	25.9 %CV	59.7
V_p: Body weight on V_p (Power)	0.830	8.04	0.699	0.961		
cov(IIV in V_c, IIV in CL)[c]	0.203[b]	48.9	0.00846	0.398	NA	NA
Residual variability proportional	0.0555	13.6	0.0407	0.0703	23.6 %CV	NA
Minimum value of the objective function = 4359.41						

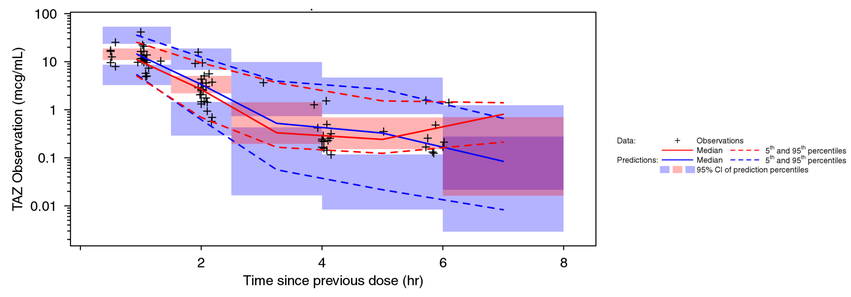
Abbreviations: CI, confidence interval; cIAI, complicated intra-abdominal infection; %CV, coefficient of variation expressed as a percentage; eGFR, estimated glomerular filtration rate; IIV, interindividual variability; MDRD, modification of diet in renal disease; NA, not applicable; NE, not estimated; %SEM, standard error of the mean expressed as a percentage.

[a] The following parameter estimates were found to be highly correlated (r^2 = 0.898).

[b] The following parameter estimates were found to be highly correlated (r^2 = 0.861).

[c] The calculated correlation coefficient (r) of the off-diagonal omegas was 0.875 with (r^2 = 0.766) for cov(IIV in V_c, IIV in CL).

Figure 2. VPC for Pediatric Data From the Tazobactam Final Population PK model



TAZ: tazobactam; Medians and percentiles are plotted at the midpoint of each time since previous dose interval

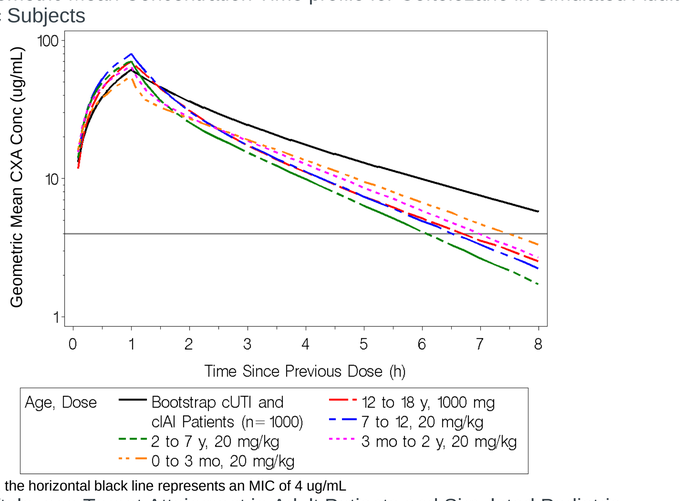
Simulations Results

- Several dosing regimens for each pediatric age group were evaluated.
- The geometric mean concentration-time profiles for simulated pediatric subjects and adults are shown in Figures 3 and 5, for ceftolozane and tazobactam, respectively, for the following dosing regimens:
  - Ages 12 to <18 years
    - 1.5 g ceftolozane/tazobactam (consisting of 1000 mg ceftolozane with 500 mg tazobactam) via a 1-hour IV infusion every 8 hours
  - Ages less than 12 years
    - 20 mg/kg ceftolozane with 10 mg/kg tazobactam via a 1-hour IV infusion every 8 hours
  - The 95th percentile of AUC and Cmax for each pediatric age group at the recommended dosing regimen was less than or equal to those in the adult population.

Results

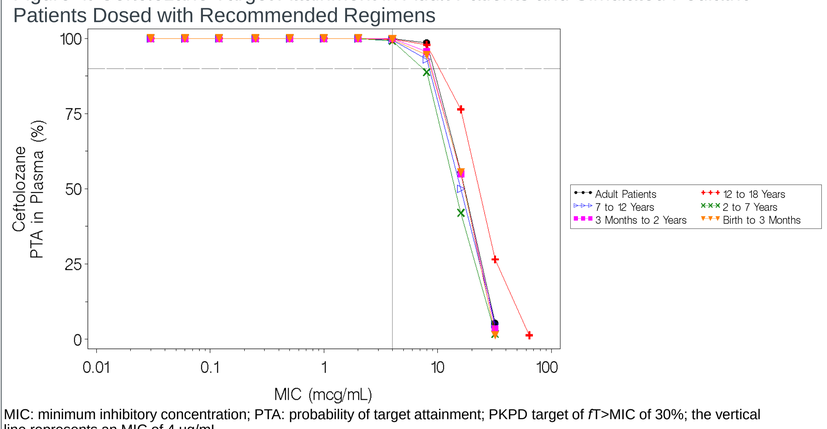
As shown in Figures 4 and 6, the ceftolozane and tazobactam PTA was ≥ 90% for adult and pediatric patients, suggesting that the selected doses will be efficacious in pediatric subjects.

Figure 3. Geometric Mean Concentration Time profile for Ceftolozane in Simulated Adult and Pediatric Subjects



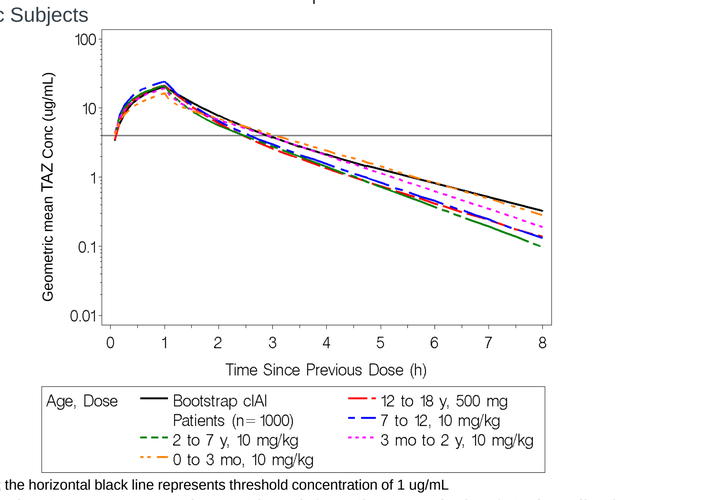
CXA: ceftolozane; the horizontal black line represents an MIC of 4 ug/mL

Figure 4. Ceftolozane Target Attainment in Adult Patients and Simulated Pediatric Patients Dosed with Recommended Regimens



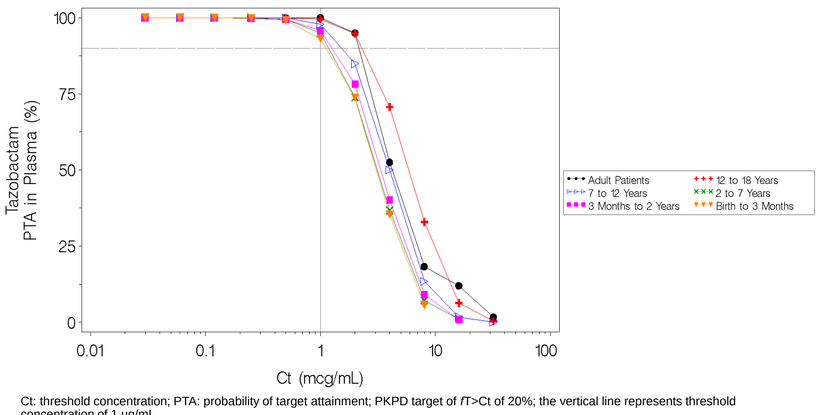
MIC: minimum inhibitory concentration; PTA: probability of target attainment; PKPD target of *f*T>MIC of 30%; the vertical line represents an MIC of 4 ug/mL

Figure 5. Geometric Mean Concentration Time profile for Tazobactam in Simulated Adult and Pediatric Subjects



TAZ: tazobactam; the horizontal black line represents threshold concentration of 1 ug/mL

Figure 6. Tazobactam Target Attainment in Adult Patients and Simulated Pediatric Patients Dosed with Recommended Regimens



Ct: threshold concentration; PTA: probability of target attainment; PKPD target of *f*T>Ct of 20%; the vertical line represents threshold concentration of 1 ug/mL

Conclusions

- Two-compartment models described the concentration-time profiles of ceftolozane and tazobactam in adults and pediatric patients well.
  - The pooled models described the pediatric data well
- The models were used for pediatric simulations and dosing regimens were chosen based on exposure and PTA.
- Based on simulations of pediatric subjects with eGFR ≥50 mL/min/1.73m^2, the following doses are recommended for evaluation in Phase 2 pediatric studies:
  - Ages 12 to <18 years: 1.5 g ceftolozane/tazobactam (1000 mg ceftolozane with 500 mg tazobactam) via a 1-h IV infusion every 8 h
  - Ages less than 12 years: 20 mg/kg ceftolozane with 10 mg/kg tazobactam via a 1-h IV infusion every 8 h (not to exceed a dose of 1000 mg ceftolozane and 500 mg tazobactam)
- The doses identified in this analysis will be further evaluated in pediatric Phase 2 cUTI and cIAI studies.

1. Zerbaxa (ceftolozane and tazobactam) [prescribing information]. Whitehouse Station, NJ, USA: Merck Sharp & Dohme Corp.; 2015.
2. Craig WA, Andes DR. Antimicrob Agents Chemother. 2013 Apr;57(4):1577-82
3. Xiao AJ et al. *Infect Dis Ther*. 2017;6(1):137-148.
4. Melchers MJ et al. Antimicrob Agents Chemother. 2016 Nov 21;60(12):7272-7279.

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