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

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 m²).
- 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 (Ci) 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

- 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 and 500 mg tazobactam) via a 1-h IV infusion every 8 hours.
  - Ages less than 12 years:
    - 20 mg/kg ceftolozane with 10 mg/kg tazobactam via a 1-h 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.

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/1.73 m², the following regimens are recommended for evaluation in Phase 2 pediatric studies:
  - Ages 12 to < 18 years:
    - 1.5 g ceftolozane/tazobactam (1000 mg ceftolozane and 500 mg tazobactam) via a 1-h IV infusion every 8 hours.
  - Ages less than 12 years:
    - 20 mg/kg ceftolozane with 10 mg/kg tazobactam via a 1-h IV infusion every 8 h 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.

References