Poster P-36

Pediatric Dose Selection of Ceftobiprole for *Staphylococcus aureus* Bacteremia, Including Right-Sided Infective Endocarditis Using Model-Based Approaches

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Background

Ceftobiprole, the active moiety of the prodrug ceftobiprole medocaril sodium (Zevtera®), is a broad-spectrum, intravenous, fifth-generation cephalosporin.

In the United States, ceftobiprole is indicated for the treatment of:

- Adult patients with *Staphylococcus aureus* bloodstream infections (bacteremia, SAB), including those with right-sided infective endocarditis
- Adult patients with acute bacterial skin and skin structure infection (ABSSSI)
- Adult patients and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP)

Ceftobiprole is not currently approved for the treatment of SAB in pediatric patients [1].

A Phase 3 randomized clinical trial is planned to evaluate the safety, tolerability, efficacy, and pharmacokinetics (PK) of ceftobiprole compared to standard-of-care treatment in pediatric patients from birth to <18 years of age with SAB, including right-sided infective endocarditis.

Objective: Conduct pharmacometric analyses to identify pediatric doses that are expected to be safe and efficacious for the Phase 3 pediatric clinical trial

Methods

A population pharmacokinetic (PK) model was developed to simulate ceftobiprole exposure in a dataset of 5,000 hypothetical patients (**Figure 1**)

Renal impairment was approximated by randomly assigning estimated glomerular filtration rate (eGFR) values.

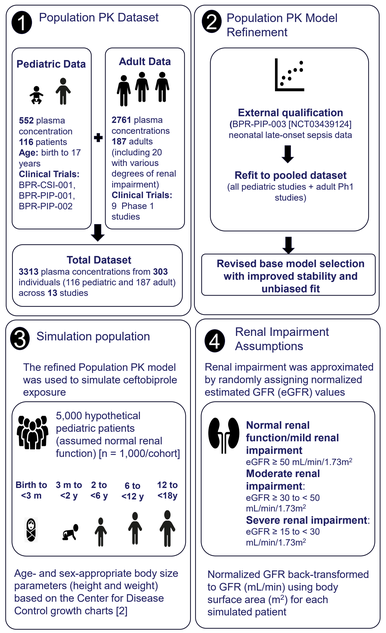
Probability of PK/pharmacodynamic (PD) target attainment (PTA) was based on:

- The PK/PD driver of efficacy of % time of dosing interval that unbound ceftobiprole plasma concentrations exceed the minimum inhibitory concentration (%fT>MIC).
- A conservative estimate of 50% fT>MIC with a MIC of 4 µg/mL was used

The approved pediatric dosing regimens for CABP [1] served as the starting point simulations. The appropriateness of the dosing regimens was considered based on:

- Exposure matching to those from the reference populations [1]:
  - Adults pooled across all Phase 3 studies (n = 765)
  - Adults in the Phase 3 SAB trial (BPR-CS-009 [NCT03137173], n = 180)
  - Pediatric patients in the pediatric Phase 3 hospital acquired bacterial pneumonia (HABP)/CABP study (BPR-PIP-002 [NCT03439124], n=29)
- PTA attainment of ≥ 90%

Figure 1. Method schematic



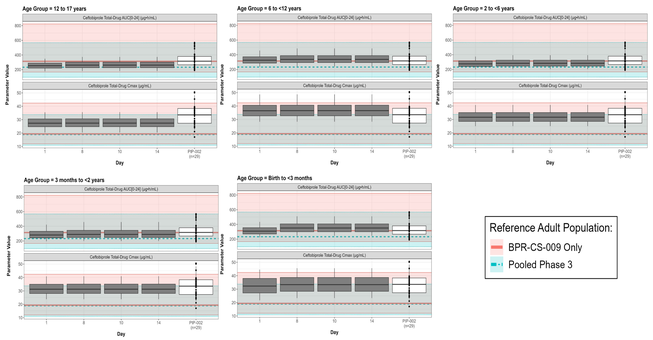
Results

- The population PK model provided an adequate and minimally biased description of the pooled data, supporting its use for pediatric exposure simulations
- The simulated pediatric area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) and maximum drug concentration (C_{max}) compared to the reference populations are shown in **Figures 2-4**

Patients with normal renal function or mild renal impairment (eGFR ≥ 50 mL/min/1.73m²) [Figure 2]:

- Across age groups, the simulated pediatric AUC_{0-24} values were contained within the distribution of the reference population values
  - Overall, there was overlap between the median pediatric values and the median values from the reference populations
- The simulated pediatric C_{max} was generally contained within the distribution of the reference population
  - Overall, the median pediatric values were higher than the median adult values. However, the C_{max} distribution overlapped the distribution of the observed C_{max} of the pediatric BRP-PIP-002 study

Figure 2. AUC_{0-24} and C_{max} distributions in pediatric patients with normal renal function and mild renal impairment (eGFR ≥ 50 mL/min/1.73m2) compared to reference populations



Patients with moderate renal impairment (eGFR ≥ 30 to < 50 mL/min/1.73m²) [Figure 3]:

- The simulated pediatric AUC_{0-24} and C_{max} values were generally contained within the distribution of the reference population values
- A wider C_{max} distribution was observed in patients birth to < 3 months, which is expected based on their renal function

Patients with severe renal impairment (eGFR ≥ 15 to < 30 mL/min/1.73m²) [Figure 4]:

- The simulated pediatric AUC_{0-24} and C_{max} values were generally contained within the distribution of the reference population values
- The pediatric population PK dataset did not contain patients less than 2 years with an eGFR < 30 mL/min/1.73m²

PTA across ages and renal function:

- PTA values at an MIC of 4 µg/mL across Days 1-14 are shown in **Table 1**
  - Normal renal function/ mild renal impairment: PTA 93.4 - 99.7%
  - Moderate renal impairment: PTA 97.4 - 100%
  - Severe renal impairment: PTA 94.5 - 100%

Figure 3. AUC_{0-24} and C_{max} distributions in pediatric patients with moderate renal impairment (eGFR ≥ 30 to < 50 mL/min/1.73m²) compared to reference populations

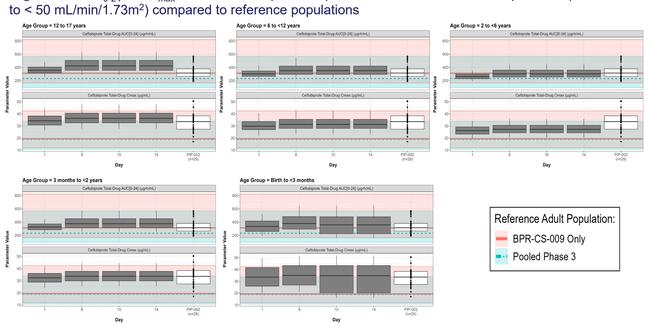
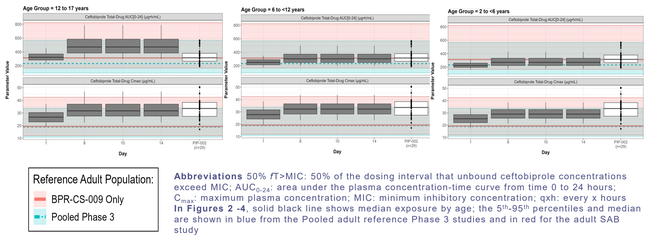


Figure 4. AUC_{0-24} and C_{max} distributions in pediatric patients with severe renal impairment (eGFR ≥15 to< 30 mL/min/1.73m2) compared to reference populations



Abbreviations 50% fT>MIC: 50% of the dosing interval that unbound ceftobiprole concentrations exceed MIC; AUC_{0-24}: area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}: maximum plasma concentration; MIC: minimum inhibitory concentration; qxh: every x hours
In Figures 2 -4, solid black line shows median exposure by age; the 5th-95th percentiles and median are shown in blue from the Pooled adult reference Phase 3 studies and in red for the adult SAB study

Table 1. PTA on Days 1 and 14 by age group and renal function, with estimate of 50% fT/MIC

Renal function description		Age group				
		≥ 12 years to< 18 years	≥ 6 years to < 12 years	≥ 2 years to < 6 years	≥ 3 months to < 2 years	Birth to < 3 months
Normal, or mild impairment	Dose	10 mg/kg* q8h	15 mg/kg*q8h	15 mg/kg*q8h	15 mg/kg q8h	15 mg/kg q12h
	Day1	94.7	97.9	93.4	94	99.7
	Day 14	94.7	97.9	93.6	94	99.7
Moderate impairment	Dose	7.5 mg/kg* q12h	7.5 mg/kg* q12h	7.5 mg/kg* q12h	10 mg/kg q12h	15 mg/kg q12h
	Day 1	100	99.9	99.7	99.8	99.6
	Day 14	100	100	99.7	99.8	97.4
Severe impairment	Dose	7.5 mg/kg† q12h	7.5 mg/kg† q24h	7.5 mg/kg† q24h	Excluded	Excluded
	Day 1	100	97.8	94.5		
	Day 14	100	98.6	96.3		

* Up to a maximum dose of 500 mg ceftobiprole (equivalent to 667 mg of ceftobiprole medocaril sodium)
† Up to a maximum dose of 250 mg ceftobiprole (equivalent to 333 mg of ceftobiprole medocaril sodium)

Conclusion

- Pharmacometric analyses support that the selected dosing regimens are expected to provide safe and efficacious exposures for pediatric patients with SAB, including right-sided infective endocarditis
- The selected regimens (**Table 2**) will be evaluated in an upcoming pediatric clinical trial assessing the safety, efficacy, and pharmacokinetics of ceftobiprole in pediatric SAB
- Patients who are less than 2 years of age with severe renal impairment (i.e., eGFR ≥ 15 to <30 mL/min/1.73m²) will not be enrolled in the study as supporting pediatric PK data for this subgroup are unavailable

Table 2. Proposed Ceftobiprole dosing regimens for pediatric SAB by age group, body weight category and renal function status (infused over 2 hours)

Renal function description	Dosing	Age group and body weight category					
		≥ 12 years to < 18 years	≥ 6 years to < 12 years	≥ 2 years to < 6 years	≥ 3 months to < 2 years	Birth to < 3 months: ≥ 4 kg	Birth to < 3 months: ≥ 3.7 to < 4 kg
Normal, or mild impairment eGFR ≥ 50 mL/min/1.73 m²	Dose	10 mg/kg*	15 mg/kg*	15 mg/kg*	15 mg/kg	15 mg/kg	10 mg/kg
	Frequency	q8h	q8h	q8h	q8h	q12h	q12h
Moderate impairment eGFR ≥ 30 to < 50 mL/min/1.73 m²	Dose	7.5 mg/kg*	7.5 mg/kg*	7.5 mg/kg*	10 mg/kg	15 mg/kg	10 mg/kg
	Frequency	q12h	q12h	q12h	q12h	q12h	q12h
Severe impairment eGFR ≥ 15 to < 30 mL/min/1.73 m²	Dose	7.5 mg/kg†	7.5 mg/kg†	7.5 mg/kg†	Excluded	Excluded	Excluded
	Frequency	q12h	q24h	q24h			

* Up to a maximum dose of 500 mg ceftobiprole (equivalent to 667 mg of ceftobiprole medocaril sodium)
† Up to a maximum dose of 250 mg ceftobiprole (equivalent to 333 mg of ceftobiprole medocaril sodium)

References

1. US Food and Drug Administration, Ceftobiprole Medocaril Sodium for Injection, 2024.https://www.fda.gov/drugs/development-resources/ceftobiprole-medocaril-sodium-injection
2. CDC growth chart https://www.cdc.gov/growthcharts/cdc-growth-charts.htm
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