Poster P - 381

Extrapolation of Adult Efficacy and Safety to Support Pediatric Use of Ceftobiprole For Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Kajal B. Larson[1], Reddy Tummala[1], Nicole C. Close[1], Christopher M. Rubino[2], Khurram Rana[1], Caeul Lim[1], Angela Tanudra[1], Sarah M. McLeod[1], Shruta Rege[1], David Altarac[1], Drew E. Lewis[1]

[1]Innoviva Specialty Therapeutics, Inc., Waltham, MA USA; [2]Institute of Clinical Pharmacodynamics, Schenectady, NY, USA

Innoviva Specialty Therapeutics, Inc.
930 Winter Street Suite 1500
Waltham, MA 02451
Kajal.Larson@istx.com

Background

ZEVTERA® (ceftobiprole medocaril sodium) is a broad-spectrum intravenous (IV) cephalosporin

In the United States, Zevtera 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)

The safety and efficacy of ceftobiprole for the treatment of pediatric patients with ABSSSI has not been established. However, ceftobiprole has been studied in 4 pediatric trials (**Table 1**)

We analyzed the available adult and pediatric data, utilizing the extrapolation framework developed under FDA E11A guidance [1] to assess whether these data could support pediatric dosing recommendations for ABSSSI

Methods

Safety

- Safety analysis focused on evaluation of adverse events (AEs) and other safety-related outcomes in pediatric patients and a comparison to the adult safety profile
- Source data included:
  - Pediatric study data (N=182 participants) from 4 completed pediatric clinical trials of ceftobiprole (birth to <18 years)
  - Adult comparator data (N=1221 participants) from 4 previous Phase 3 studies in adults, including those with ABSSSI
- AEs were evaluated by severity, relatedness, seriousness, and those leading to treatment discontinuation, study discontinuation, or death
- Comparisons are descriptive only; no formal statistical testing was performed

Pharmacometrics

- A population pharmacokinetic (PK) model, which was qualified with neonatal data, was used to characterize ceftobiprole disposition in plasma
- Model-based simulations, using a dataset of 5000 hypothetical patients aged birth to < 18 years were conducted. Impact of renal impairment was also assessed
- Probability of PK-pharmacodynamic (PD) target attainment (PTA) analyses were conducted using % time of dosing interval that unbound ceftobiprole plasma concentrations exceed a minimum inhibitory concentration (%*f*T>MIC)
- Dosing regimens were considered appropriate if:
  - PTA was ≥ 90% using %*f*T>MIC of 40% at an MIC of 4 µg/mL
  - Predicted steady-state area under the curve (AUC) and maximum plasma concentration (C_{max}) that predominantly fall within the 5th and 95th percentiles of the adult values

Table 1. Pediatric trials conducted to date with ceftobiprole

Study Phase / Study Number / NCT Number; Brief Description	Number of Patients
Phase 1 / CSI-1006 / NCT01026636; An open-label study to evaluate the single-dose PK and safety of ceftobiprole in pediatric subjects ≥ 3 months to < 18 years of age undergoing treatment with systemic antibiotics	N=64 Ceftobiprole: n=64
Phase 1 / BPR-PIP-001 / NCT02527681; An open-label study to evaluate the single-dose PK and safety of ceftobiprole in neonate and infant patients aged up to 3 months undergoing treatment with systemic antibiotics	N=15 Ceftobiprole: n=15
Phase 3 / BPR-PIP-002 / NCT03439124; A multicenter, randomized, Investigator-blind, active-controlled study to evaluate the safety, tolerability, PK and efficacy of ceftobiprole in pediatric patients aged from 3 months to <18 years with HAP or CAP requiring hospitalization	N=138 Ceftobiprole: n=94 Comparator: n=44
Phase 3 / BPR-PIP-003 / NCT05856227; A multicenter, open-label, single-arm, multiple-dose study to evaluate the safety, PK, and efficacy of ceftobiprole in term and pre-term neonates and infants up to 3 months of age with late-onset sepsis	N = 9 Term = 3 Pre-term = 6

Acknowledgements:
We are grateful to the patients and their families for their participation in the trials, and to the site staff and CRO partners for their efforts on the trials. We also thank Basilea Pharmaceutica Ltd. for their support and for providing access to the data that made these analyses possible.

Safety Results

- The safety outcomes are shown in **Table 2**
- No consistent age-related trend (**Figure 1**): the 6- to < 12-year group, with the highest predicted C_{max}, had the lowest TEAE incidence, 11 (26.2%)
- Most common pediatric TEAEs were gastrointestinal, 26 (14.3%) vs 304 (24.9%) in adults, mainly vomiting 13 (7.1%) and diarrhea 4 (2.2%); no Hy's law cases; no renal events, convulsions or *C. difficile* infection in the available pediatric dataset (**Figure 2**)
- Exposure-adjusted event rates per 100 patient-days (**Table 3**) were similar for TEAEs (22.7 vs 25.0) and lower for treatment-related AEs (4.0 vs 5.4) and related SAEs (0.1 vs 0.4)
- Post-marketing: 2 pediatric reports; 1 with non-serious nausea/vomiting that resolved

Table 2. Comparison of safety outcomes between pediatric patients and adults

Outcome	Pediatric (N = 182) n (%)	Adult (N = 1221) n (%)
Patients with ≥ 1 TEAE	73 (40.1)	785 (64.3)
Patients with ≥ 1 severe TEAE	8 (4.4)	213 (17.4)
Patients with ≥ 1 treatment-related TEAE	20 (11.0)	330 (27.0)
Patients with ≥ 1 SAE	19 (10.4)	217 (17.8)
Patients with ≥ 1 treatment-related SAE	1 (0.5)	33 (2.7)
TEAE leading to treatment discontinuation	5 (2.7)	96 (7.9)
TEAE leading to death	0	114 (9.3)
Patients with ≥ 1 AESI	22 (12.1)	292 (23.9)

Figure 1. Comparison of treatment-emergent adverse events (TEAEs) by age groups and severity

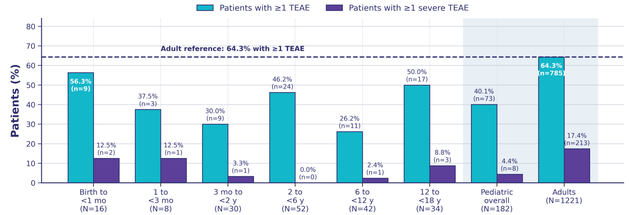


Figure 2. Comparison of adverse events of special interest (AESI) between pediatric and adult patients

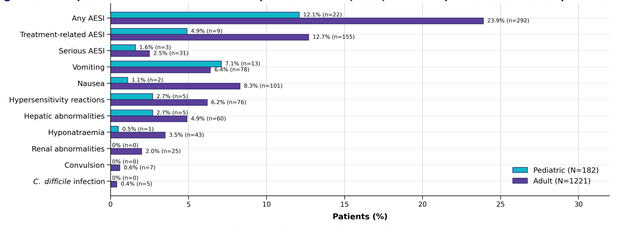


Table 3. Exposure-adjusted incidence rates (EAIR), per 100 patient-days

Event category	Pediatric (N = 182) 668 patient-days	Adult (N = 1221) 11,967 patient-days
Total exposure (patient-days)	668	11,967
Overall TEAEs	22.7	25.0
Treatment-related AEs	4.0	5.4
SAEs	4.3	3.3
Related SAEs	0.1	0.4
AESIs	4.3	3.9
Related AESIs	1.8	1.9

Pharmacometric Results

- Population PK dataset: 552 plasma concentrations from 116 pediatric patients, pooled with 2761 concentrations from 187 adults across 9 Phase 1 studies (20 with renal impairment)
- Diagnostics (VPCs, parameter precision, shrinkage) showed the model captured both central tendency and variability, with no systematic bias
- The exposure distributions by renal function (**Figure 3**) were used to assess adequacy of dosing regimens in relation to 3 reference populations: pooled adult Phase 3, adult ABSSSI trial, and pediatric CABP study (BPR-PIP-002)

Figure 3. PK exposures by renal function category at doses shown in Table 4

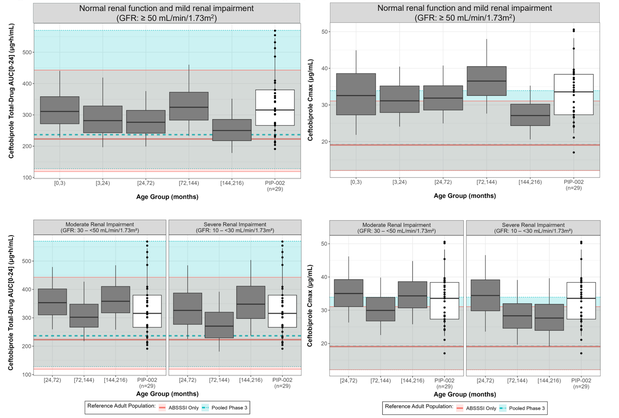


Table 4. Percent probability of target attainment using a *f*T>MIC of 40% with a MIC of 4 µg/mL

	Birth to <3 mo	3 mo to <2 years	2 to <6 years	6 to <12 years	12 to <18 years
	Normal renal function or mild renal impairment (GFR: ≥ 50 mL/min/1.73m²)				
Dose	15 mg/kg q12h[a]	15 mg/kg q8h	15 mg/kg q8h[a]	15 mg/kg q8h[a]	10 mg/kg q8h[a]
PTA	100	99	99.6	99.7	99.1
	Moderate Renal Impairment (GFR: 30 to < 50 mL/min/1.73m²)				
Dose	N/A		10 mg/kg q12h	7.5 mg/kg q12h	7.5 mg/kg q12h
PTA			100	100	100
	Severe Renal Impairment (GFR: 10 to < 30 mL/min/1.73m²)				
Dose	N/A		10 mg/kg q24h[b]	7.5 mg/kg q24h[b]	7.5 mg/kg q12h[b]
PTA			100	99.7	100

All regimens administered as a 2-h infusion with a maximum allowable dose of 500 mg regardless of patient's weight unless otherwise specified. No dosage regimens are proposed for patients less than 2 years of age with moderate or severe renal impairment. All doses are in ceftobiprole equivalent;
[a] Infants weighing <4 kg received 10 mg/kg. [b] Maximum dose is 250 mg.

For patients with normal renal function or mild renal impairment (GFR of ≥50 mL/min/1.73m²):

- Simulated AUC_{0-24} values were contained within those observed in the pediatric trial (BPR-PIP-002) and remained within the adult AUC_{0-24} distribution
- Simulated pediatric C_{max} exceeded adult distributions, especially in those 6 years to < 12 years of age; however, the median C_{max} was within the pooled adult Phase 3 data and comparable to the observed pediatric data

For patients with moderate (GFR of 30 to < 50 mL/min/1.73m²) or severe renal impairment (GFR of 10 to < 30 mL/min/1.73m²):

- Simulated distributions were mostly contained were within the distribution of the observed AUC_{0-24} from BPR-PIP-002
- Median ceftobiprole C_{max} was at or above the 95th percentile of the ABSSSI adult distribution and generally comparable to the observed pediatric data

Conclusions

- An extrapolation strategy is a scientifically justifiable approach to informing dosing for pediatric ABSSSI (**Figure 4**)
- Safety analyses identified no new pediatric safety signals; the pediatric safety profile was generally consistent with the known adult safety profile
  - Fewer TEAEs, lower treatment-related and discontinuation rates, no deaths in children
  - No consistent age-related trend in TEAE incidence or severity
- Using modeling and simulations, the doses shown in **Table 5** were found to yield exposures that were generally comparable to those observed in the pediatric Phase 3 CABP trial (BPR-PIP-002) with high PTA (**Table 4**)
- While ceftobiprole is currently approved in adults with ABSSSI, extrapolation represents a viable strategy to inform potential pediatric labeling updates

Figure 4. Scientific rationale supporting extrapolation of ceftobiprole data from adults to pediatric patients with ABSSSI

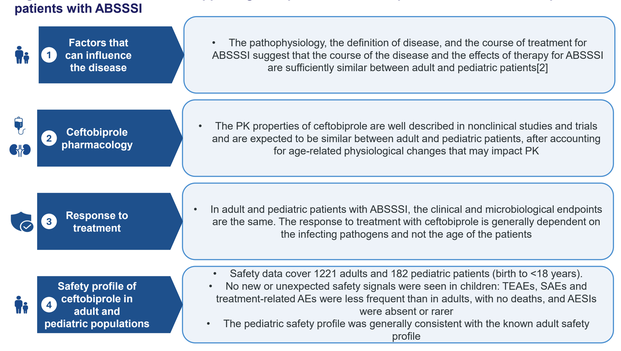


Table 5. Potential ceftobiprole dosage regimens for pediatric patients by age and renal function for ABSSSI

Age	Creatinine clearance (mL/min/1.73 m²)[a]	Dose (mg/kg)[b]	Interval
Term neonates and infants < 3 months with body weight < 4 kg	≥ 50	10	every 12 hours
Term neonates and infants < 3 months with body weight ≥ 4 kg	≥ 50	15	every 12 hours
Infants aged ≥ 3 months to children < 2 y	≥ 50	15	every 8 hours
Infants aged 2 to children < 6 y	≥ 50	15	every 8 hours
	30 to <50	10	every 12 hours
	10 to <30	10[c]	every 24 hours
Children aged 6 to <12 y	≥ 50	15	every 8 hours
	30 to <50	7.5	every 12 hours
	10 to <30	7.5[c]	every 24 hours
Adolescents aged 12 to <18 years	≥ 50	10	every 8 hours
	30 to <50	7.5	every 12 hours
	10 to <30	7.5[c]	every 12 hours

Note: No dosage regimens are proposed for patients less than 2 years of age with moderate or severe renal impairment. All doses are in ceftobiprole equivalent;
[a] Calculated using the Schwartz formula for pediatric patients.
[b] All doses administered over 2 hours with a maximum dose of ceftobiprole is 500 mg (equivalent to 667 mg of ceftobiprole medocaril sodium), unless otherwise noted.
[c] Maximum dose is 250 mg (equivalent to 333 mg of ceftobiprole medocaril sodium)

Reference:
[1] U.S. Food and Drug Administration, U.S. Department of Health and Human Services. E11A Pediatric Extrapolation (Final Guidance) 2024.
[2] Department of Health and Human Services US , Food and Drug Administration. Guidance for Industry, Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment 2013.

Presented at IDWeek 2026, Washington DC